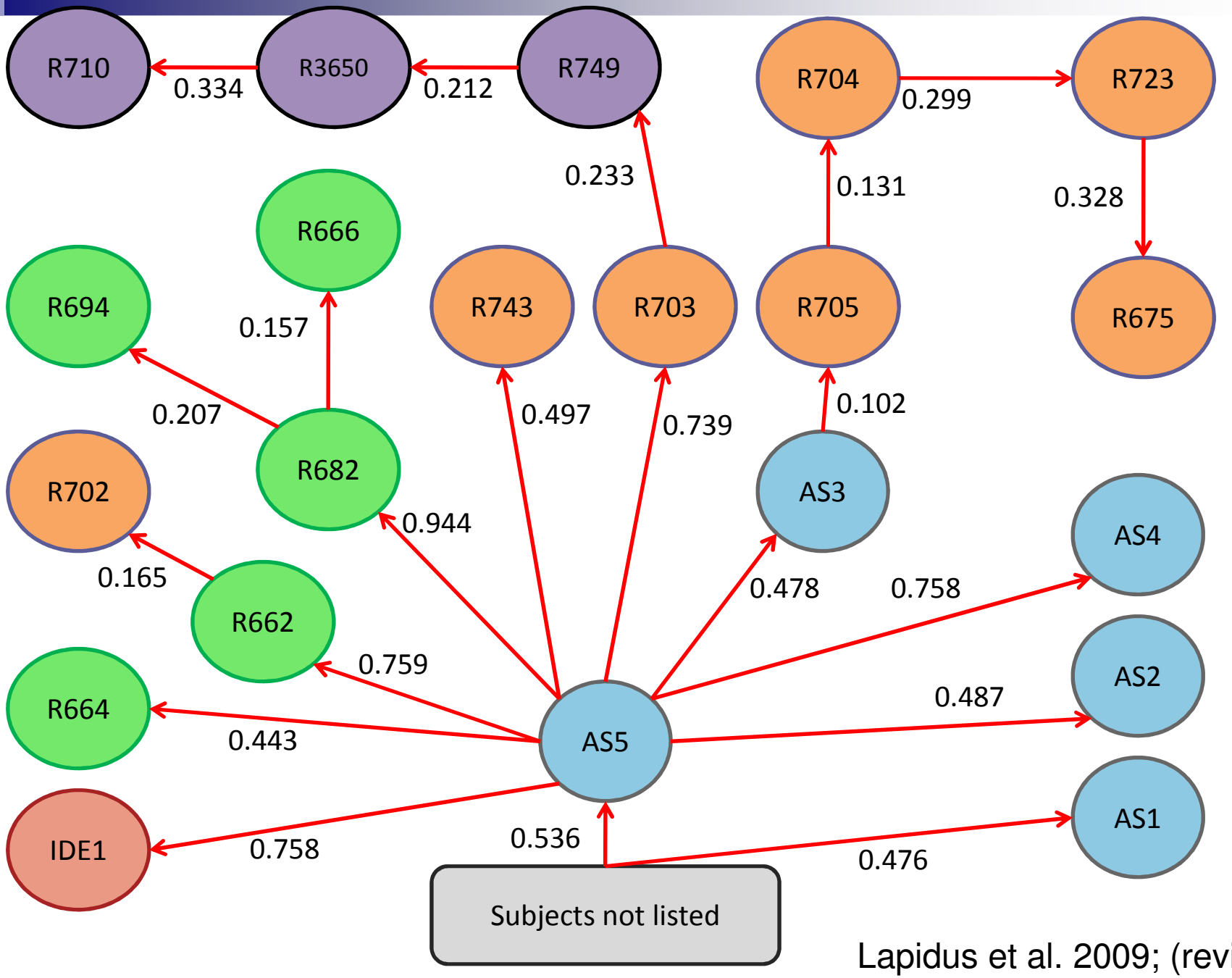
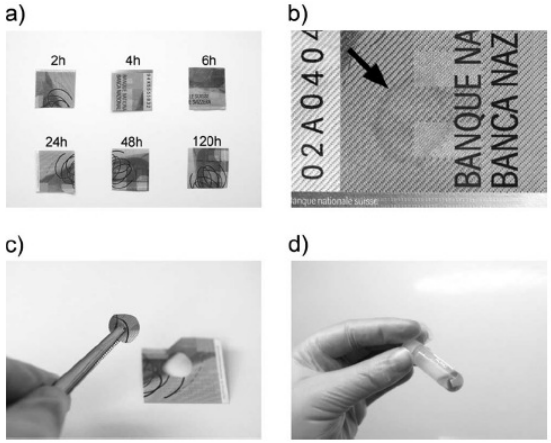
Transmission et mesures de limitation de la diffusion du virus

- 3 modes de transmission de la grippe
  - Goûtelettes (>8 µm) émises lors de la toux
    - Mode d'action principal
    - Faible rayon d'action (<2.5m)
  - Aérosols – droplet nuclei (<5 µm)
    - Grand rayon d'action
  - Surfaces contaminées
- La part respective de ces différents modes de transmission dans les infections est inconnue



Lapidus et al. 2009; (revised)

Transmission via les surfaces contaminées: survie du virus sur des billets de banque.



Thomas A et al. Appl Environ Microbiol 2008;74:3002

Survie du virus issues de sécrétions respiratpoires d'enfants infectés dans une forme infectieuse au moins 48 heures

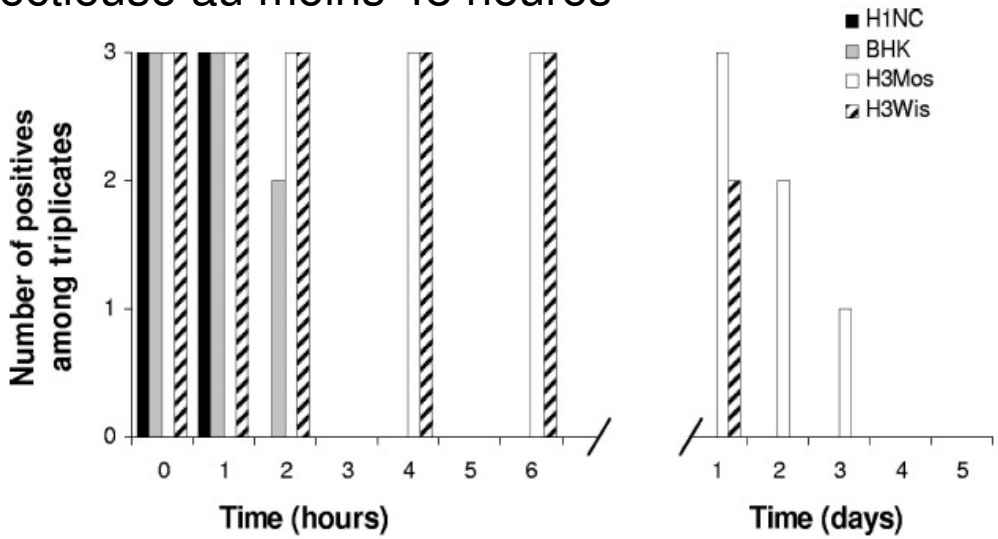


FIG. 2. Duration of infectiousness of four different influenza virus subtypes after inoculation onto banknotes at room temperature. The following viral suspensions were used in triplicate for each experiment: influenza A/New Caledonia/20/99 (H1N1) virus (H1NC) at a concentration of 2.8×10^5 $TCID_{50}$/ml; influenza B/Hong Kong/335/2001 virus (BHK) at a concentration of 1.6×10^4 $TCID_{50}$/ml; influenza A/Moscow/10/99 (H3N2) virus (H3Mos) at a concentration of 8.9×10^6 $TCID_{50}$/ml; and influenza A/Wisconsin/67/2005 (H3N2) virus (H3Wis) at a concentration of 5×10^4 $TCID_{50}$/ml.

Transmission par les surfaces (suite)

- Echantillonnage des surfaces dans 8 foyers hébergeant des enfants malades
- Recherche de virus grippal par RT-PCR
- 92 prélèvements, sur 14 types de surfaces
- Viabilité virale non évaluée

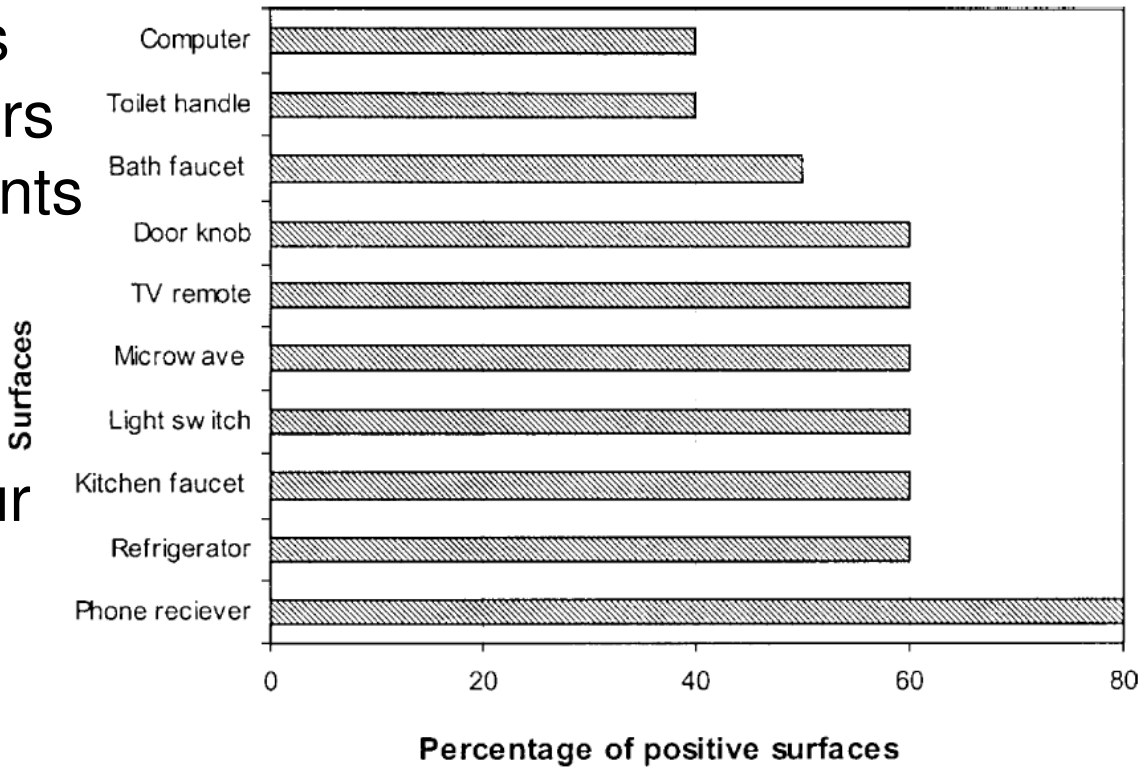
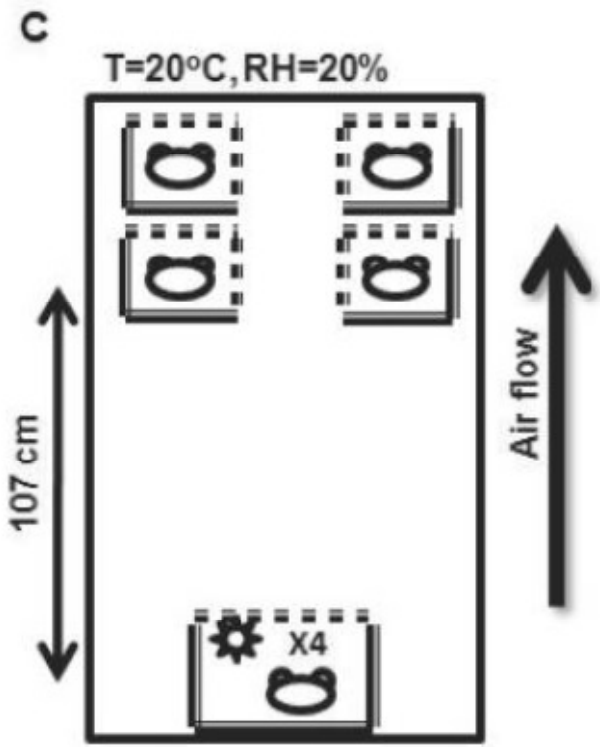
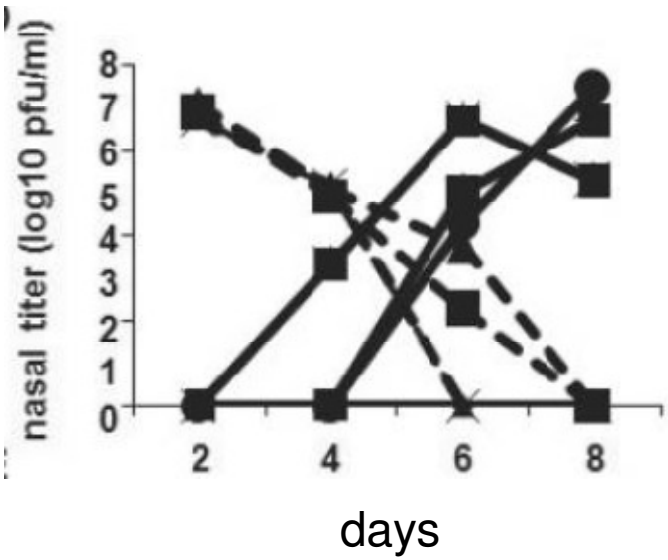


Figure 6 Occurrence of influenza A virus on surfaces in homes with ill children.

Boone SA et al. J Infection 2005;51:103

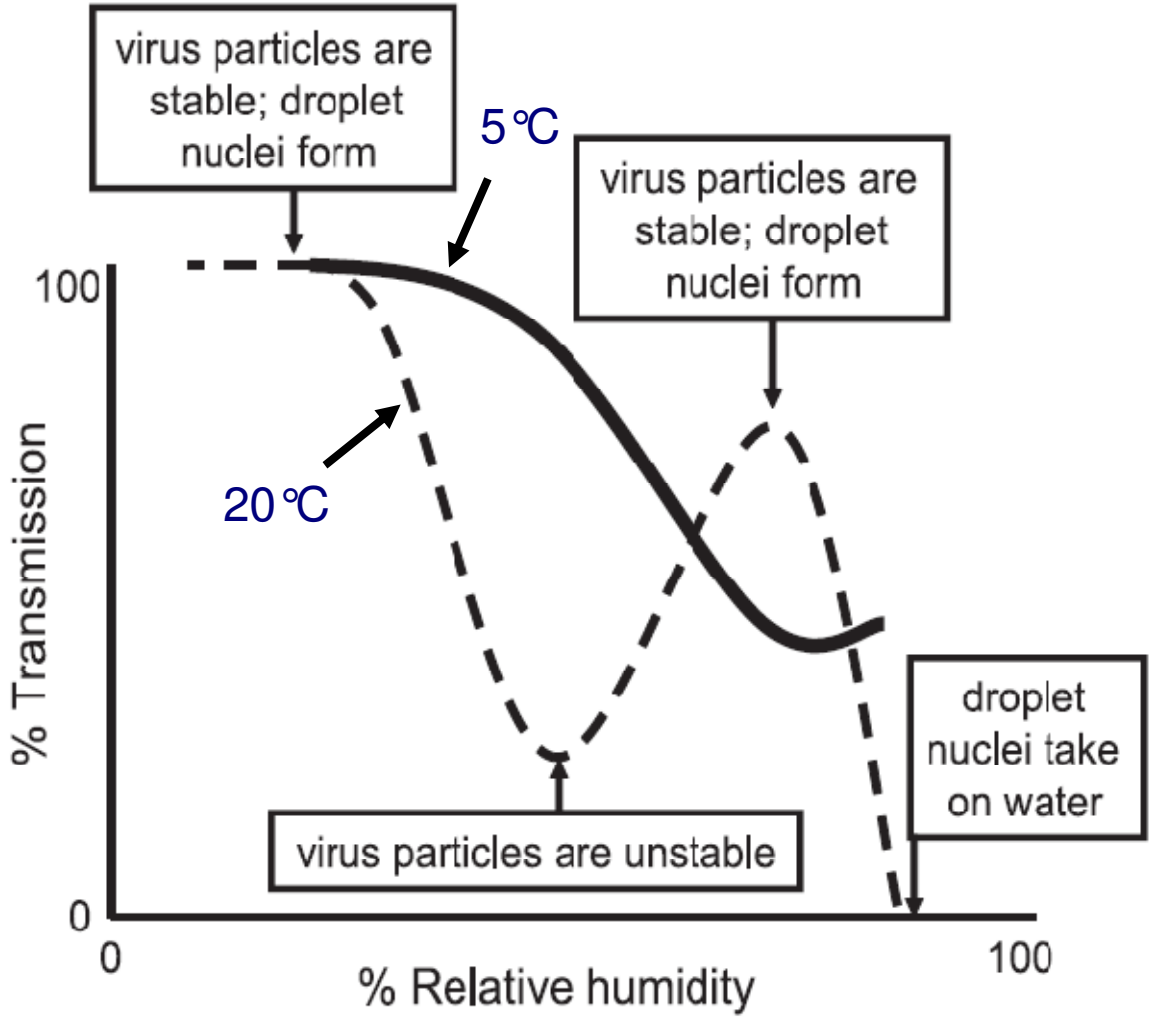
Transmission via aérosols- (cochons d'inde)





Mubareka S. J Infect Dis 2009;199:858

Conditions expérimentales de la transmission



Lowen A et al. Plos Pathogens 2007;3:e51

Mesure de limitations: masques

- GripMask : Un essai randomisé en groupes parallèles pour évaluer l'efficacité du masque chirurgical dans la réduction de la transmission secondaire de la grippe dans les foyers.

Intervention dans l'essai

- Intervention
  - Port du masque chirurgical par les malades du foyer
  - Aussi souvent que possible à chaque fois qu'une autre personne non malade du foyer fréquente le même espace (pièce, voiture, ….)
  - Pour une durée maximale de 5 jours par malade
  - Changé après 3 heures d'utilisation consécutive et éliminé de façon « propre »

Objectifs

- Objectif primaire
  - Diminution du nombre de cas de syndromes grippaux dans les foyers randomisés dans le groupe masque vs contrôle.
- Objectifs secondaires
  - Mesurer les tolérance et adhérence
  - Dans un sous ensemble de foyers: taux d'infection

Principaux critères d'inclusion

- Foyers de taille 3-8 dans lequel,
  - Le patient index (1er malade de la grippe du foyer) a plus de 5 ans,
  - consulte pendant la période d'épidémie de syndromes grippaux telle que définie par le réseau Sentinelles,
  - pour des symptômes débutant depuis moins de 48 heures
    - Fièvre >=37.8°C
    - Toux

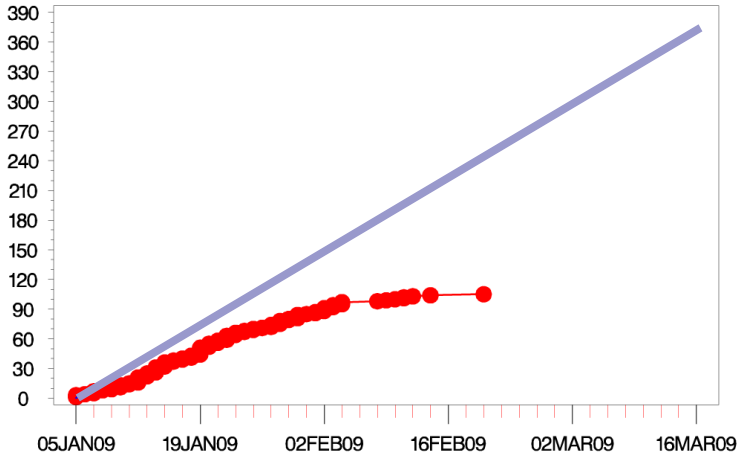
- Le test rapide pour le patient index est positif A

Critères de jugement

- Taux « d'attaque » secondaire, c.a.d. la proportion de sujets par bras qui développeront un syndrome grippal dans les 7 jours
  - Fièvre >37.8°c ET toux ou mal de gorge
- Critères secondaires
  - Acceptabilité du port du masque
  - En fonction de la durée entre début des symptômes et intervention
  - En utilisant définition de cas secondaire plus sensible (fièvre non obligatoire)
- 372 foyers nécessaires pour montrer une diminution de 24% à 14% du taux d'attaque secondaire

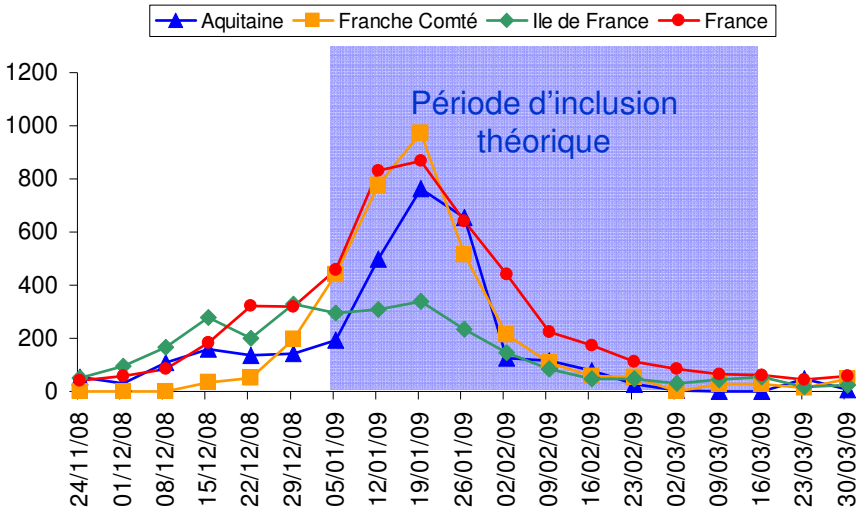
GripMask

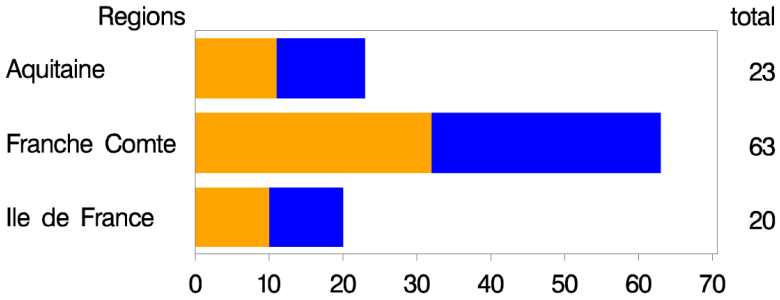
courbe des inclusions au 16MAR09
105 inclus, 372 attendus



APHP et UPMC/U707 Confidential

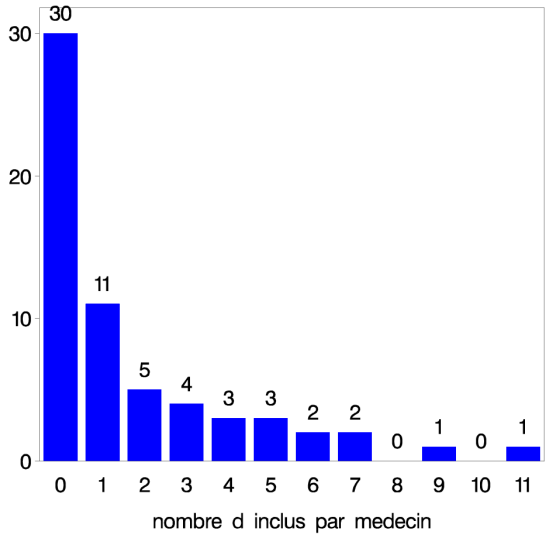
Incidence hebdomadaire syndromes grippaux (source réseau Sentinelles)





GripMask

Inclusions par medecin au 06APR09



APHP et UPMC/U707 Confidential

Baseline Characteristics

	Masque	Control	P Value
Index patient - no	**52**	**53**	
Age – mean ± SD	25 ± 5	28 ± 5	0.42
<15 – no (%)	19 (37)	16 (30)	0.49
Sex ratio (M/F)	26/26	29/24	0.63
Vaccinated – no (%)	0 (0)	2 (4)	0.50
Current smoker yes – no (%)	15 (29)	2 (4)	0.001
Symptoms duration – no (%)			
<6	0 (0)	1 (2)	0.86
6-12	8 (15)	8 (15)	
13-18	13 (25)	10 (19)	
19-24	8 (15)	13 (25)	
25-36	11 (21)	11 (21)	
37-48	10 (19)	9 (17)	
Not available	2 (4)	1 (2)	
Number of household contacts			
Total: Mean ± SD	2.9 ± 1.1	3.0 ± 1.0	0.31
≥15 yrs: Mean ± SD	2.1 ± 0.9	1.8 ± 0.8	0.16
<15 yrs: Mean ± SD	0.8 ± 0.7	1.2 ± 1.0	0.05
Household contacts - no	**148**	**158**	
Age – mean ± SD	29 ± 19	25 ± 17	0.06
<15 yrs – no (%)	41 (28)	62 (39)	0.03
Sex ratio (M/F)	73/75	80/78	0.82
Vaccinated – no (%)	14 (9)	6 (4)	0.06
Current smoker yes – no (%)	24 (16)	20 (13)	0.38

Cas secondaires

	Masque	Contrôle	p
Critère principal	21/148 (14%)	23/158 (15%)	1.0
Définition plus « sensible »	35/148 (24%)	37/158 (23%)	1.0

Cas secondaires (si apparaît après 1j)

	Masque	Contrôle	p
Critère principal	11/126 (8%)	13/135 (9%)	0.83
Définition plus « sensible »	24/126 (19%)	25/135 (19%)	1.0

Port du masque – gêne

- 40 patients (77%) ont ressenti une gêne

Difficultés respiratoires	33% (17)
Chaleur	42% (22)
Humidité	31% (16)
Irritation	13% (7)
N'aime pas être vu avec le masque	29% (15)
Douleur	7.7% (4)

Port du masque - caractéristiques

	Moyenne (écart-type)	Range
Nombre total de masques utilisés	10 (7)	0-30
Nombre de masques utilisés par jour	2.5 (1.7)	0-6
Nombre de jours où le masque a été porté	3.8 (1.7)	0-7
Durée du port du masque par jour (h)	3.7 (2.7)	0-14

Annals of Internal Medicine | ARTICLE

Facemasks and Hand Hygiene to Prevent Influenza Transmission in Households

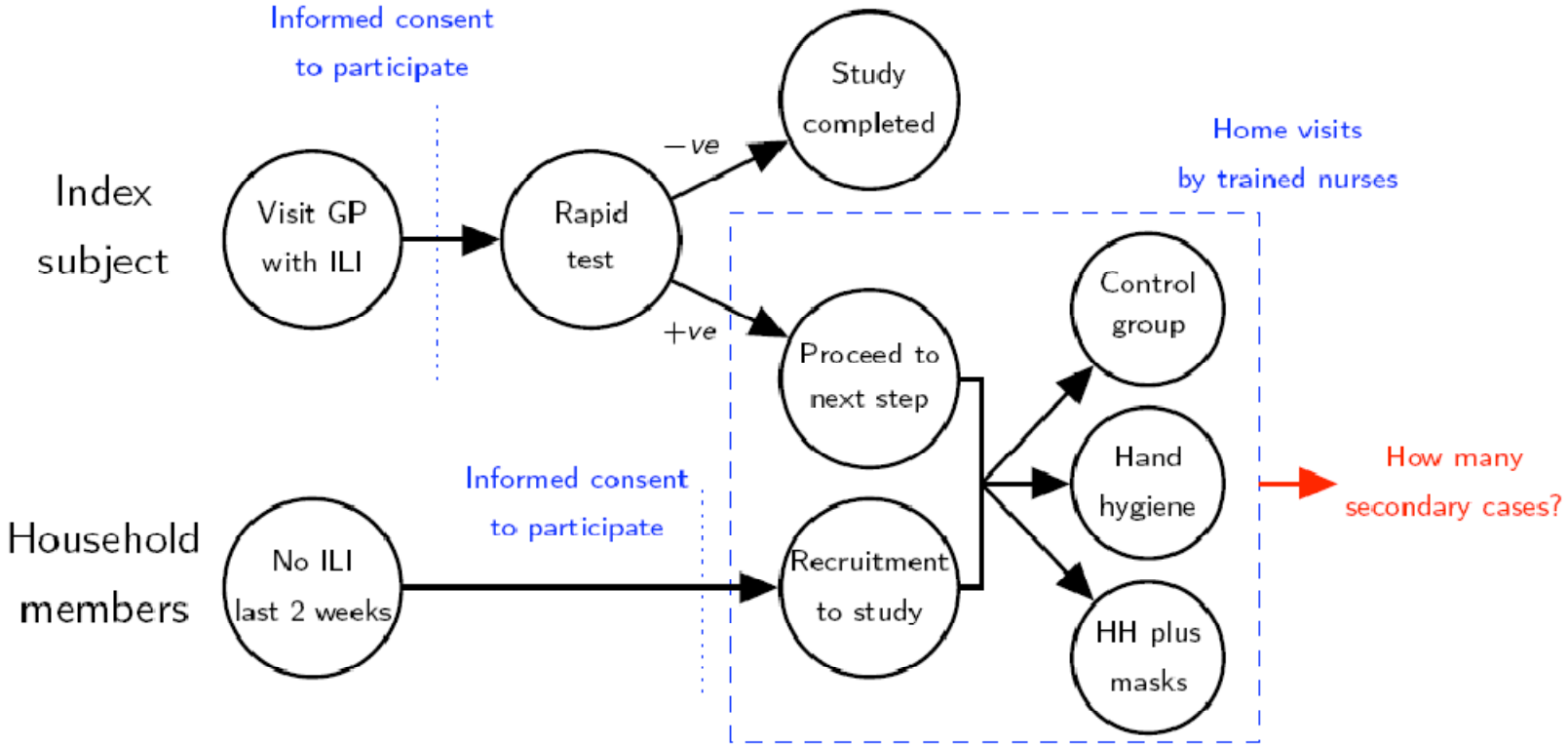
A Cluster Randomized Trial

Benjamin J. Cowling, BSc, PhD; Kwok-Hung Chan, BSc, PhD; Vicky J. Fang, BSc, MPhil; Calvin K.Y. Cheng, BSc, MMedSci; Rita O.P. Fung, BNS; Winnie Wai, BNS; Joey Sin, BNS; Wing Hong Seto, MBBS; Raymond Yung, MBBS, MPH; Daniel W.S. Chu, MBBS; Billy C.F. Chiu, MBBS; Paco W.Y. Lee, MBBS; Ming Chi Chiu, MBBS; Hoi Che Lee, MBBS; Timothy M. Uyeki, MD, MPH; Peter M. Houck, MD; J.S. Malik Peiris, MBBS, DPhil; and Gabriel M. Leung, MD, MPH

Case-ascertainment design – index cases with influenza-like illness recruited from outpatient clinics

- Any 2+ ILI symptoms or signs (broad definition).
- Onset of symptoms within the last 48 hours.
- Live with at least 2 other people.
- No other household members have had ILIs within the past 2 weeks.

NPI RCT – Study design



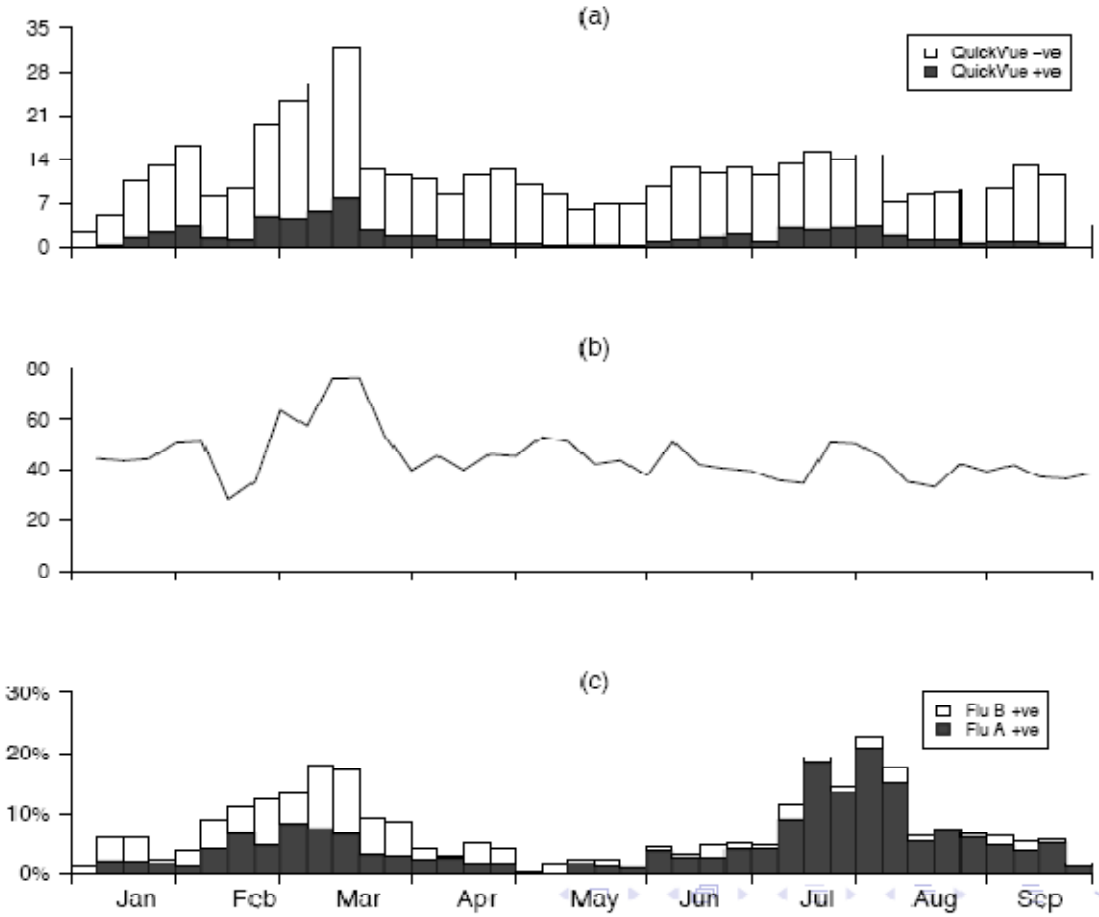
306 households successfully followed up with lab-confirmed index case; in compliance with the protocol 47 households with RT-PCR-confirmed co-index cases at the time of the intervention were excluded from subsequent analyses.

Recruitment vs flu activity – 2008 main study

Study recruitment rate (subjects per day)

Community ILI circulation (ILI cases per 1,000 GP consultations)

Positive laboratory isolates (QMH)



Main results (I.T.T.) – secondary attack ratios

Table: Secondary attack ratios in the contacts of 259 analyzed households.

	Secondary attack ratio (95% CI)*						p-value†
	Control *(n=279)*		Hand hygiene *(n=257)*		Mask+HH *(n=258)*		
Lab-confirmed influenza	0.10	(0.07, 0.14)	0.05	(0.03, 0.09)	0.07	(0.04, 0.11)	0.22
Clinical influenza(1)	0.19	(0.14, 0.24)	0.16	(0.12, 0.21)	0.21	(0.16, 0.26)	0.45
Clinical influenza(2)	0.05	(0.03, 0.08)	0.04	(0.02, 0.07)	0.07	(0.04, 0.11)	0.28

* By the exact binomial method.

† By Pearson chi-square test adjusted for within-household correlation.

(1) is at least 2 of fever$\geq$37.8°C, cough, headache, sore throat, aches or pains in muscles or joints.

(2) is fever$\geq$37.8°C plus cough or sore throat.

SARs for timely intervention

Table: Secondary attack ratios in the contacts of 154 analyzed households where the intervention was applied within 36 hours of symptom onset in the index case.

	Secondary attack ratio (95% CI)*						p-value†
	Control *(n=183)*		Hand hygiene *(n=130)*		Mask+HH *(n=149)*		
RT-PCR-confirmed influenza	0.12	(0.08, 0.18)	0.05	(0.02, 0.11)	0.04	(0.01, 0.09)	0.04
Clinical influenza(1)	0.22	(0.17, 0.29)	0.11	(0.06, 0.17)	0.18	(0.12, 0.25)	0.03
Clinical influenza(2)	0.07	(0.03, 0.11)	0.04	(0.01, 0.09)	0.07	(0.04, 0.13)	0.52

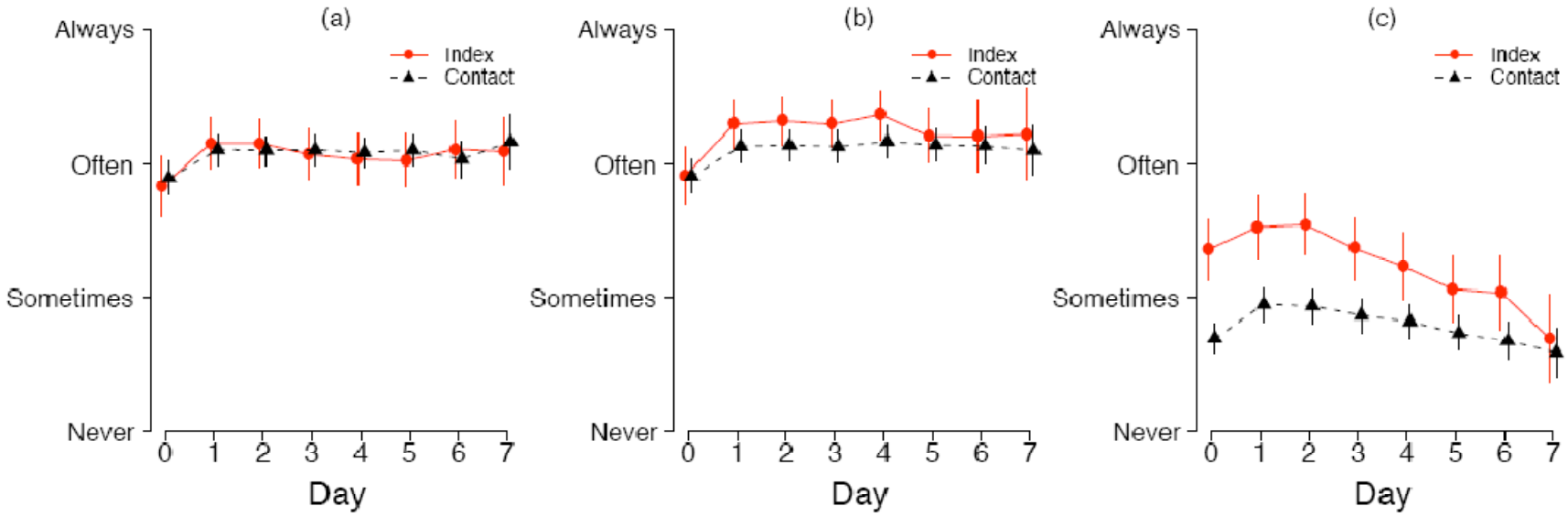
* By the exact binomial method.

† By Pearson chi-square test adjusted for within-household correlation.

(1) is at least 2 of fever $\geq 37.8^{\circ}$C, cough, headache, sore throat, aches or pains in muscles or joints.

(2) is fever $\geq 37.8^{\circ}$C plus cough or sore throat.

Adherence to interventions



(a) Reported frequency of hand washing with liquid hand soap/alcohol hand rub in the hand hygiene arm;

(b) Reported frequency of hand washing with liquid hand soap/alcohol hand rub in the mask+HH arm;

(c) Reported frequency of face mask use in the mask+HH arm.

Face Mask Use and Control of Respiratory Virus Transmission in Households

C. Raina MacIntyre, Simon Cauchemez, Dominic E. Dwyer, Holly Seale, Pamela Cheung, Gary Browne, Michael Fasher, James Wood, Zhanhai Gao, Robert Booy, and Neil Ferguson

Emerging Infectious Diseases 2009;15:233

Critères d'inclusion

- Foyers avec au moins 2 adultes
- Exposition des adultes à un enfant index (fièvre et signes respiratoires)
- 3 bras
  - Contrôle
  - Masque chirurgical porté par adultes à chaque fois que même pièce que enfant
  - Masque « P2 » (filtrant) porté par adultes à chaque fois que même pièce que enfant
- Suivi 15 jours, contact journalier des foyers (évaluation compliance)
- Prélèvements virologiques des sujets symptomatiques
- 2 saisons successives

CRITERE DE JUGEMENT PRINCIPAL : Syndrome grippal – pas de réduction significative

Table 4. Intention-to-treat analysis used in the study*

Data	Control group, no. (%)	All masks			Surgical masks			P2 masks		
		No. (%)	RR (95% CI)†	p value†	No. (%)	RR (95% CI)†	p value†	No. (%)	RR (95% CI)†	p value†
By house	n = 50	n = 93			n = 47			n = 46		
ILI	12 (24)	25 (27)	1.12 (0.62–2.03)	0.84	15 (32)	1.33 (0.70–2.54)	0.50	10 (22)	0.91 (0.43–1.89)	0.81
By individual	n = 100	n = 186			n = 94			n = 92		
ILI	16 (16)	33 (18)	1.11 (0.64–1.91)	0.75	19 (20)	1.29 (0.69–2.31)	0.46	14 (15)	0.95 (0.49-1.84)	1
Laboratory confirmed infections										
Influenza A	0	3 (2)			1 (1)			2 (2)		
Influenza B	0	1 (0.5)			0			1 (1)		
RSV	1 (1)	1 (0.5)			0			0		
hMPV	0	0			0			0		
Adenoviruses	0	2 (1)			0			2 (2)		
PIV‡	1 (1)	1 (0.5)			1 (1)			0		
Coronaviruses§	1 (1)	0			0			0		
Rhinoviruses	0	5 (3)			3 (3)			2 (2)		
Enteroviruses	0	0			0			0		
Picornoviruses	0	1 (0.5)			0			1 (1)		
Total	3 (3)	14 (8)	2.51 (0.74–8.5)	0.19	6 (6)	2.13 (0.55–8.26)	0.32	8 (9)	2.90 (0.79–10.6)	0.12

*RR, relative risk; CI, confidence interval; ILI, influenza-like illness; RSV, respiratory syncytial virus; hMPV, human metapneumovirus; PIV, parainfluenza

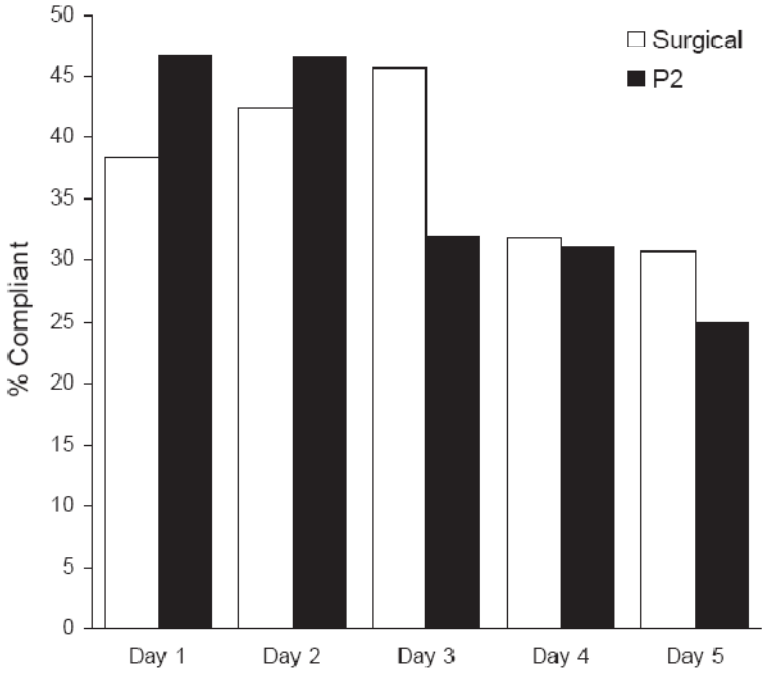


Figure 2. Compliance with face mask use by day over 5 consecutive days during the study, Sydney, New South Wales, Australia, 2006 and 2007 winter influenza seasons.

Table 3. Problems with face use reported by participants in the study, Sydney, New South Wales, Australia, 2006 and 2007 winter influenza seasons.

Reported problem	Surgical mask users, no. (%), n = 94	P2 mask users, no. (%), n = 92	p value
None	46 (49)	42 (46)	0.66
Uncomfortable	16 (17)	14 (15)	0.74
Forgot to wear it	8 (9)	8 (9)	0.96
Child did not like it	6 (6)	8 (9)	0.55
Other	18 (19)	20 (22)	0.66

Loeb et al. JAMA 2009;302:17

Table 2. Comparison of Laboratory-Confirmed Influenza Between the Surgical Mask and N95 Respirator Groups

	No. (%)		Absolute Risk Difference, % (95% CI)	*P* Value
	Surgical Mask (n = 212)	N95 Respirator (n = 210)		
Laboratory-confirmed influenza[a]	50 (23.6)	48 (22.9)	–0.73 (–8.8 to 7.3)	.86
RT-PCR influenza A	5 (2.4)	1 (0.5)	–1.88 (–4.13 to 0.36)	.22
RT-PCR influenza B	1 (0.5)	3 (1.4)	0.96 (–0.89 to 2.81)	.37
≥4-Fold rise in serum titers A/Brisbane/59/2007 (H1N1)[b]	25 (11.8)	21 (10)	–1.79 (–7.73 to 4.15)	.55
≥4-Fold rise in serum titers A/Brisbane/10/2007 (H3N2)[b]	42 (19.8)	49 (23.3)	3.52 (–4.32 to 11.36)	.38
≥4-Fold rise in serum titers B/Florida/4/2006[b]	15 (7.1)	19 (9.0)	2.0 (–3.0 to 7.17)	.46
≥4-Fold rise in serum titers A/TN/1560/09 (H1N1)[b]	17 (8.0)	25 (11.9)	3.89 (–1.82 to 9.59)	.18

Conclusion

- Dans le contexte de la grippe saisonnière
  - Pas d'efficacité documentée
  - Compliance au port du masque = facteur clé
  - L'hygiène des mains apparaît plus efficace que le masque
- Ne peut pas être extrapolé *ex abrupto* au contexte pandémique