Web Appendix

for(j in 1:N.Sample){

```
# Virus Interference Review by the Test-negative study
# American Journal of Epidemiology
# Confidence Intervals by Bootstrap
# Dataset could be downloaded from:
https://www.dropbox.com/s/ayk27b6he9zwwsv/VirIntRev_Fig3Data.dat?dl=0
library(metafor)
setwd() # set working directory where the dataset is saved
load("VirIntRev_Fig3Data.dat")
# dataset of 44 observations and 7 variables
# dataset orders are the same with shown in Figure 3
# author: first author
# VE.FluNeg: point estimates of VE by influenza negative controls
# VE.FluNeg.ll: lower confidence intervals of VE by influenza negative controls
# VE.FluNeg.ul: upper confidence intervals of VE by influenza negative controls
# VE.ORVPos: point estimates of VE by other respiratory virus positive controls
# VE.ORVPos.ll: lower confidence intervals of VE by other respiratory virus positive controls
# VE.ORVPos.ul: upper confidence intervals of VE by other respiratory virus positive controls
#=======Calculate beta and SE of covariate based on
VE=========
VirIntRev$Beta.FluNeg <- log(1-VirIntRev$VE.FluNeg/100)
VirIntRev$SE.FluNeg <- (log(1-VirIntRev$VE.FluNeg.ll/100) - log(1-
VirIntRev$VE.FluNeg.ul/100))/qnorm(0.975)/2
VirIntRev$Beta.ORVPos <- log(1-VirIntRev$VE.ORVPos/100)</pre>
VirIntRev$SE.ORVPos <- (log(1-VirIntRev$VE.ORVPos.ll/100) - log(1-
VirIntRev$VE.ORVPos.ul/100))/qnorm(0.975)/2
#=======Calculate delta VE and Confidence
Intervals========
VirIntRev$Delta.VE <- round(VirIntRev$VE.FluNeg - VirIntRev$VE.ORVPos, 0)</pre>
## Delta VE as difference between VE(FLU-) and VE(ORV+)
set.seed(0725)
N.Sample <- 1000 # 1000 times bootstrap
Delta.VE.ll <- Delta.VE.ul <- rep(NA, N.Sample)
## 1000 times bootstrap estimates of confidence intervals
Meta.Delta.VE.Mean <- Meta.Delta.VE.SE <- rep(NA, N.Sample)
## Calculate mean and standard error of each Delta VE for meta-analysis
# Bootstrap
for(i in 1:nrow(VirIntRev)){
```

```
VE.FluNeg <- (1-exp(rnorm(1000, VirIntRev$Beta.FluNeg[i], VirIntRev$SE.FluNeg[i]))*100
  VE.ORVPos <- (1-exp(rnorm(1000, VirIntRev$Beta.ORVPos[i], VirIntRev$SE.ORVPos[i])))*100
  Delta.VE.ll[j] <- quantile(VE.FluNeg - VE.ORVPos, 0.025, na.rm=TRUE)
  Delta.VE.ul[j] <- quantile(VE.FluNeg - VE.ORVPos, 0.975, na.rm=TRUE)
  Meta.Delta.VE.Mean[j] <- mean(VE.FluNeg - VE.ORVPos)</pre>
  Meta.Delta.VE.SE[j] <- sd(VE.FluNeg - VE.ORVPos)
}
VirIntRev$Delta.VE.ll[i] <- round(mean(Delta.VE.ll), 0)</pre>
VirIntRev$Delta.VE.ul[i] <- round(mean(Delta.VE.ul), 0)</pre>
VirIntRev$Meta.Delta.VE.Mean[i] <- round(mean(Meta.Delta.VE.Mean), 0)</pre>
VirIntRev$Meta.Delta.VE.SE[i] <- round(mean(Meta.Delta.VE.SE), 3)</pre>
}# end of loop
VirIntRev$Delta.VE.CI <- paste(VirIntRev$Delta.VE, "% (", VirIntRev$Delta.VE.II, "%, ",
VirIntRev$Delta.VE.ul, "%)", sep="")
VirIntRev$Delta.VE.CI
# Meta-analysis
index.AorB <- c(2, 3, 4, 9, 10, 11, 12, 13, 14, 16, 17, 18, 19, 20, 21, 25, 26, 27, 29, 30, 31)
## Pool Delta VE against influenza A or B
Meta <- list()
Meta$Model <- rma(yi = Meta.Delta.VE.Mean, sei = Meta.Delta.VE.SE, data =
VirIntRev[index.AorB, ], method="FE")
Meta$Delta.VE <- round(c(Meta$Model$b), 0)</pre>
Meta$Delta.VE.SE <- Meta$Model$se
Meta$Delta.VE.ll <- round(Meta$Delta.VE+qnorm(0.025)*Meta$Delta.VE.SE, 0)
Meta$Delta.VE.ul <- round(Meta$Delta.VE+qnorm(0.975)*Meta$Delta.VE.SE, 0)
Meta$Delta.VE.CI <- paste(Meta$Delta.VE, "% (", Meta$Delta.VE.ll, "%, ", Meta$Delta.VE.ul, "%)",
sep="")
Meta$Delta.VE.CI
```

end

Web Table 1. Summary of clinical case definitions and related symptoms from included published studies.

Study	Clinical case definition	Clinical case definition symptoms			
Blyth et al.	ILI	At least 1 acute respiratory symptom or sign plus either a documented fever ≥37.5°C or his			
		of fever in the past 96 hours			
Cowling et al.	ARI	Fever measured ≥38°C with any respiratory symptom such as cough, runny nose, or sore throat			
Feng et al.	ARI	Any two of the following reported symptoms: fever, cough, sore throat, rhinorrhea, and			
		congestion			
Grijalva et al.	Admission with pneumonia	Admission with community-acquired pneumonia			
Kelly et al.	ILI	A documented fever with oral (or aural) temperature \geq 38°C (or axillary temperature $>$ 37.5°C),			
		with at least one acute respiratory symptom or sign			
Levy et al.	ILI	An acute upper respiratory tract infection characterised by fever, cough, and fatigue			
Nunes et al.	ILI	The European Union ILI case definition (Sudden onset of symptoms; at least one of four			
		systemic symptoms: fever or feverishness, malaise, headache, myalgia; at least one of three			
		respiratory symptoms: cough, sore throat, shortness of breath)			
Pierse et al.	SARI ILI	ILI: a history of fever (or measured temperature of ≥38°C) and cough			
		SARI: ILI + hospitalisazion			
Sullivan et al.	ILI	Fever, cough and fatigue			
Sundaram et al.	ARI	Included fever/feverishness or cough during most seasons			

Suzuki et al.	ILI	Sudden onset of fever and at least one of the following symptoms: cough, runny nose, sore		
		throat, headache, myalgia, or fatigue		
van Doorn et al.	ARI or ILI	ILI: an acute onset of symptoms (full development of typical symptoms in ≤4 days) including a		
		rectal temperature of at least 38 °C and at least one respiratory or systemic symptom (i.e.		
		cough, nasal catarrh, sore throat, frontal headache, retrosternal pain, myalgia)		
		ARI: an acute respiratory illness other than ILI, such as acute sinusitis or pneumonia, and with		
		at least one of the following symptoms: coughing, rhinorrhea or sore throat		

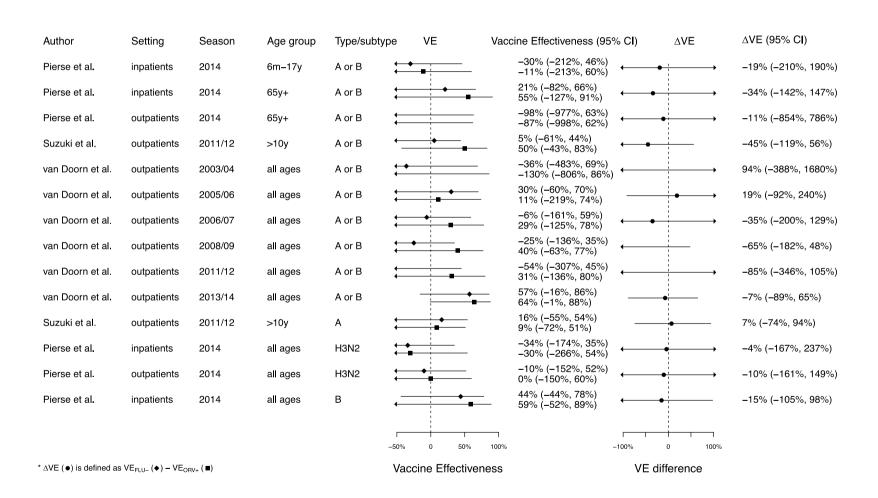
ARI: acute respiratory infection; ILI: influenza-like illness; SARI: severe acute respiratory infection

Web Figure 1. Comparison of all specific VE estimates by flu- and ORV+ control groups, restricted by 95% CI range for VE_{FLU-} of ≤ 100 percentage points. VE: Vaccine effectiveness; CI: confidence interval; ORV+: other respiratory virus positive

Author	Setting	Season	Ago group	Typo/subtypo	VE Vaco	oino Effortivonoss (059/ CI_A\/E*	ΔVE (95% C I)
	-		Age group		ve vacc	cine Effectiveness (9	95% CI) AVE	
Blyth et al.	outpatients (ED)	2008–2012	6–59m	A or B		66% (32%, 83%) 86% (38%, 97%)	_	-1% (-35%, 36%)
Blyth et al.	outpatients (ED)	2008–2012	<2y	A or B		86% (35%, 97%) 52% (0%, 77%)		0% (-49%, 50%)
Blyth et al.	outpatients (ED)	2008–2012	2y+	A or B	_	55% (–4%, 81%) 62% (43%, 74%)		-3% (-60%, 61%)
Cowling et al.	inpatients	2009–2013	6m–17y	A or B		63% (39%, 77%) 47% (42%, 52%)	-	–1% (–24%, 25%)
Feng et al.	outpatients	2010–2013	all ages	A or B	*	51% (44%, 57%) 40% (29%, 49%)	+	-4% (-12%, 4%)
Feng et al.	outpatients	2010/11	all ages	A or B	-	39% (24%, 50%) 50% (36%, 61%)	•	1% (–15%, 18%)
Feng et al.	outpatients	2011/12	all ages	A or B	-	59% (46%, 69%) 51% (43%, 58%)	-• <u>1</u>	-9% (-26%, 8%)
Feng et al.	outpatients	2012/13	all ages	A or B	+ +	57% (48%, 64%) 58% (48%, 66%)	•	– 6% (– 17%, 5%)
Feng et al.	outpatients	2010–2013	6m–5y	A or B	*	57% (46%, 66%) 45% (33%, 54%)	+	1% (–12%, 15%)
Feng et al.	outpatients	2010–2013	6–17y	A or B	-	45% (29%, 57%) 36% (22%, 48%)	-	0% (–17%, 18%)
Feng et al.	outpatients	2010–2013	18–49y	A or B	-	42% (24%, 55%)		-6% (-26%, 15%)
Feng et al.	outpatients	2010–2013	50y+	A or B	-	35% (11%, 52%) 35% (0%, 58%)		0% (–33%, 39%)
Grijalva et al.	inpatients	2010–2012	all ages	A or B	-	57% (32%, 73%) 63% (40%, 77%)	-	-6% (-35%, 22%)
Kelly et al.	outpatients	2008	6–59m	A or B	-	87% (8%, 98%) 86% (–3%, 98%)	-	1% (–71%, 84%)
Levy et al.	outpatients	2010–2012	all ages	A or B	*	53% (40%, 63%) 59% (39%, 72%)	-	-6% (-24%, 16%)
Levy et al.	outpatients	2010	all ages	A or B		68% (35%, 85%) 79% (53%, 91%)		-11% (-47%, 20%)
Levy et al.	outpatients	2011	all ages	A or B ←	-	52% (1%, 77%) 34% (–79%, 76%)		18% (–48%, 132%)
Levy et al.	outpatients	2012	all ages	A or B	—	49% (30%, 63%) 60% (34%, 76%)		-11% (-36%, 18%)
Nunes et al.	outpatients	2012/13	all ages	A or B		68% (21%, 87%) 82% (48%, 94%)		-14% (-61%, 25%)
Pierse et al.	inpatients	2014	all ages	A or B	-	42% (16%, 60%) 38% (–10%, 65%)		4% (-33%, 55%)
Pierse et al.	outpatients	2014	all ages	A or B	—	56% (35%, 70%) 59% (33%, 75%)	-	-3% (-29%, 26%)
Pierse et al.	outpatients	2014	6m–17y	A or B	<u></u>	80% (48%, 93%) 82% (43%, 94%)	_	-2% (-38%, 36%)
Pierse et al.	inpatients	2014	18–64y	A or B		55% (27%, 73%) 53% (–9%, 79%)	<u> </u>	2% (–37%, 64%)
Pierse et al.	outpatients	2014	18–64y	A or B		47% (16%, 66%) 47% (5%, 71%)		0% (–38%, 46%)
Sullivan et al.	outpatients	2012	all ages	A or B		23% (–4%, 43%) 24% (–12%, 49%)		-1% (-37%, 40%)
Sundaram et al.	outpatients (ED) & UC & AC	2004/05–2009/10	5m–5y	A or B	—	48% (31%, 61%) 50% (33%, 63%)	-	-2% (-23%, 19%)
Sundaram et al.	outpatients (ED) & UC & AC	2004/05–2009/10	50y+	A or B	—	44% (25%, 58%) 43% (18%, 60%)	-	1% (–24%, 29%)
van Doorn et al.	outpatients	2003–2014	all ages	A or B	-	21% (–1%, 39%) 64% (49%, 75%)	-•-	-43% (-68%, -20%)
van Doorn et al.	outpatients	2007/08	all ages	A or B	-	77% (39%, 92%) 95% (82%, 99%)		-18% (-58%, 3%)
van Doorn et al.	outpatients	2010/11	all ages	A or B		50% (5%, 74%) 80% (53%, 92%)		-30% (-76%, 7%)
van Doorn et al.	outpatients	2012/13	all ages	A or B	——	57% (19%, 78%) 90% (73%, 96%)		-33% (-72%, -7%)
Blyth et al.	outpatients (ED)	2008–2012	6–59m	Α		80% (42%, 93%) 78% (35%, 93%)		2% (–37%, 48%)
Cowling et al.	inpatients	2009–2013	6m-17y	Α		57% (29%, 74%) 63% (33%, 80%)	_	-6% (-38%, 29%)
Pierse et al.	inpatients	2014	all ages	Α		42% (15%, 61%) 36% (–14%, 65%)	_	6% (-34%, 60%)
Pierse et al.	outpatients	2014	all ages	Α	—	53% (30%, 69%) 57% (29%, 74%)	_	-4% (-33%, 28%)
Sullivan et al.	outpatients	2012	all ages	Α _	<u> </u>	15% (–17%, 38%) 13% (–32%, 42%)		2% (–41%, 51%)
Sullivan et al.	outpatients	2012	all ages	A (not H1)	<u></u>	13% (-20%, 36%) 11% (-34%, 41%)		2% (–42%, 52%)
Cowling et al.	inpatients	2009–2013	6m–17y	H1N1		72% (39%, 87%) 75% (41%, 89%)	_	-3% (-38%, 32%)
Feng et al.	outpatients	2010–2013	all ages	H1N1	- +	63% (51%, 72%) 65% (53%, 74%)	•	–2% (–17%, 13% <u>)</u>
Pierse et al.	inpatients	2014	all ages	H1N1		62% (38%, 77%) 57% (14%, 79%)	-	5% (–28%, 51%)
Pierse et al.	outpatients	2014	all ages	H1N1		59% (36%, 74%)	_	-3% (-31%, 28%)
Cowling et al.	inpatients	2009–2013	6m–17y	H3N2	•	62% (34%, 78%) 37% (–26%, 68%)		-8% (-76%, 68%)
Feng et al.	outpatients	2010–2013	all ages	H3N2	÷	45% (-25%, 76%) 39% (31%, 47%)	•	– 5% (– 17%, 7%)
Blyth et al.	outpatients (ED)	2008–2012	6–59m	В		44% (34%, 52%) 48% (–12%, 76%)		-5% (-69%, 54%)
Cowling et al.	inpatients	2009–2013	6m–17y	В	-	53% (9%, 80%) 69% (42%, 83%)	_	5% (-28%, 51%)
Feng et al.	outpatients	2010–2013	all ages	В	+	64% (19%, 84%) 50% (42%, 58%)	-	-2% (-14%, 10%)
Pierse et al.	outpatients	2014	all ages	В	-	52% (43%, 60%) 65% (19%, 85%)		2% (–49%, 63%)
Sullivan et al.	outpatients	2014	all ages	В	-	63% (5%, 86%) 53% (5%, 77%)		-3% (-49%, 63%)
Guinvan et al.	σαιραιιστιιο	LU 1 L	uii ayes	J	-	56% (–1%, 81%)		–∪ /o (– ∪/ /o, ∪0/o)
					 		•	-4% (-10%, 2%)
				-50%	0 50% 100%		-100 % 0 100%	
+ ME (-) 1 . C	NE (1) NE (1)			Vacci	ine Effectiveness	3	VE difference	

^{*} $\Delta VE\left(ullet
ight)$ is defined as $VE_{FLU-}\left(ullet
ight) - VE_{ORV+}\left(ullet
ight)$

Web Figure 2. Comparison of all specific VE estimates by flu- and ORV+ control groups, restricted by 95% CI range for VE_{FLU-} of >100 percentage points. VE: Vaccine effectiveness; CI: confidence interval; ORV+: other respiratory virus positive



Web Table 2. Summary of estimates of covariates included in meta-regression.

Covariate	OR (95%CI)	p value
Univariate analysis		
Setting (compared with inpatient)		
Outpatient	1.27 (1.01, 1.60)	0.043
Mixed	1.37 (1.05, 1.79)	0.021
Age group (compared with adults)		
Children	0.76 (0.65, 0.89)	0.001
Elderly	0.95 (0.78, 1.15)	0.602
All ages	0.55 (0.44, 0.68)	< 0.001
Single season	0.57 (0.44, 0.73)	< 0.001
Viral shedding within 4 days	1.08 (0.89, 1.33)	0.431
Number of ORVs tested	1.37 (1.08, 1.74)	0.011
Control group (compared with flu-negative)		
ORV-positive as control group	0.89 (0.72, 1.11)	0.293
pan-negative as control group	0.97 (0.79, 1.20)	0.804
Multivariate analysis		
Setting (compared with inpatient)		
Outpatient	1.32 (1.01, 1.71)	0.040
Mixed	1.73 (1.17, 2.55)	0.006
Age group (compared with adults)		
Children	0.78 (0.66, 0.91)	0.002
Elderly	1.02 (0.82, 1.27)	0.861
All ages	0.88 (0.59, 1.32)	0.540
Single season	0.40 (0.24, 0.67)	< 0.001
Control group (compared with flu-negative)		
ORV-positive as control group	0.92 (0.80, 1.06)	0.235
pan-negative as control group	0.99 (0.87, 1.14)	0.925

ORV: other respiratory viruses; OR: odds ratio; CI: confidence interval