Web Appendix

```
#####################################################################
# 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$VE.ORVPos/100)
VirIntRev$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)
## 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)){
  for(j in 1:N.Sample){
```

```
  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)
  Meta.Delta.VE.SE[j]   <- sd(VE.FluNeg - VE.ORVPos)
 }

 VirIntRev$Delta.VE.ll[i] <- round(mean(Delta.VE.ll), 0)
 VirIntRev$Delta.VE.ul[i] <- round(mean(Delta.VE.ul), 0)

 VirIntRev$Meta.Delta.VE.Mean[i]    <- round(mean(Meta.Delta.VE.Mean), 0)
 VirIntRev$Meta.Delta.VE.SE[i] <- round(mean(Meta.Delta.VE.SE), 3)

}# end of loop

VirIntRev$Delta.VE.CI <- paste(VirIntRev$Delta.VE, "% (", VirIntRev$Delta.VE.ll, "%, ",
VirIntRev$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)
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 history 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 ≥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

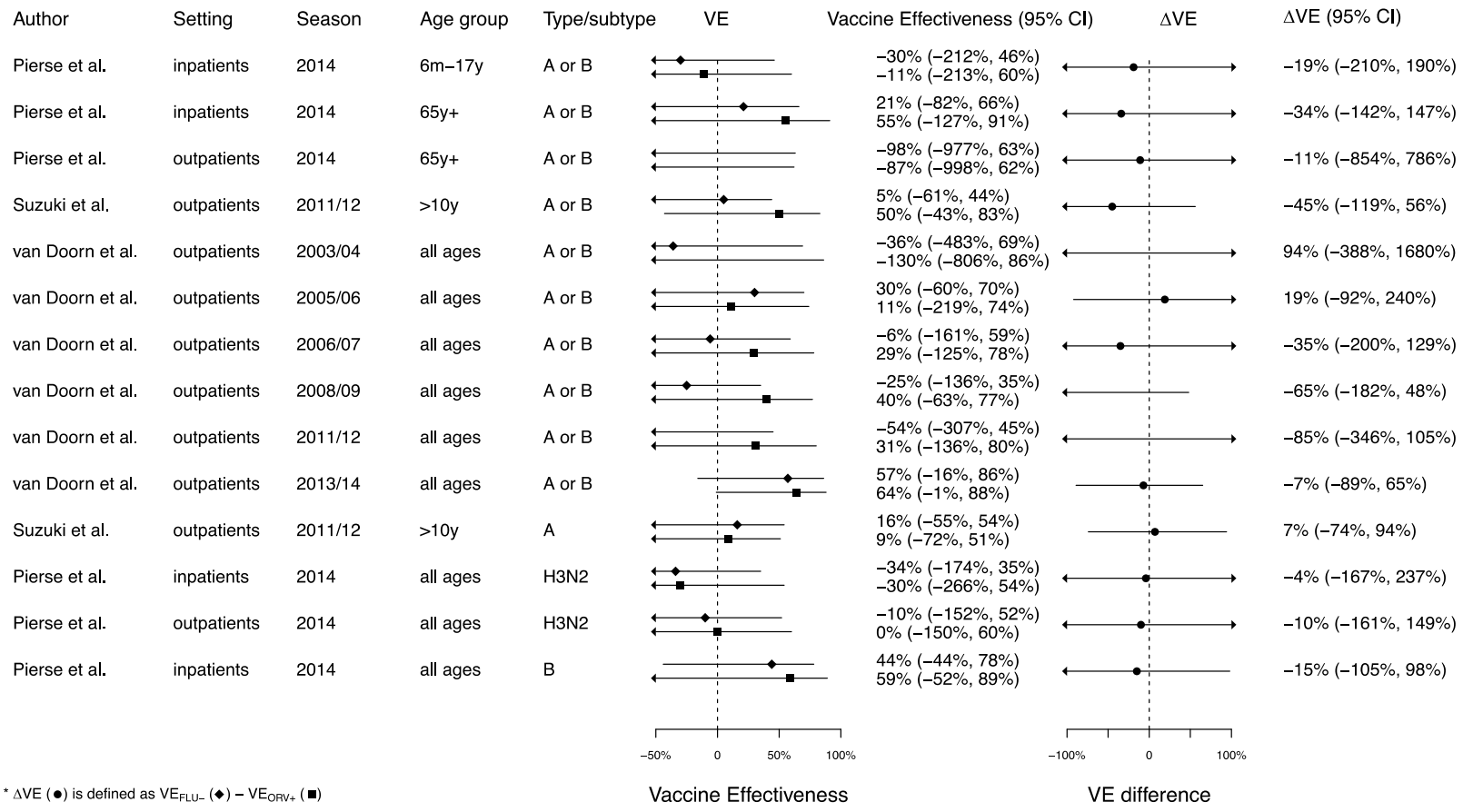
Suzuki et al.	ILI	Sudden onset of fever and at least one of the following symptoms: cough, runny nose, sore throat, headache, myalgia, or fatigue
van Doorn et al.	ARI or ILI	ILI: an acute onset of symptoms (full development of typical symptoms in ≤4 days) including a rectal temperature of at least 38 °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

* ΔVE (●) is defined as VE_{FLU-} (◆) – VE_{ORV+} (■)

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



* ΔVE (●) is defined as VE_{FLU-} (◆) – VE_{ORV+} (■)

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