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#####R SCRIPT: Reduction in antimicrobial use in weaned pigs through
#an intervention program designed to support veterinarians' adherence
#to the clinical practice guideline on Streptococcus suis!!!!!!!!!!!!!!

#load packages
library(tibble)
library(SciViews)
library(ggplot2)
library(imager)
library(lme4)
library(lmerTest)
library(gamlss)
library(dplyr)
library(viridis)
library(ggrepel)
library(ordinal)
library(writexl)
library(tidyverse)
library(tidyr)

#FUNCTIONS
#alternative ln transformatio function so 0 is not -inf
lnn<-function(x){ln(x+((x^2) + 1)^(1/2))}

#reverse the in operation
`%notin%` <- Negate(`%in%`)
#afrounding functie
round.off <- function(x, digits=2)
{ posneg = sign(x)
  z = trunc(abs(x) * 10 ^ (digits + 1)) / 10
  z = floor(z * posneg + 0.5) / 10 ^ digits
  return(z) }

# Developing 5 colors to use in graphs
plasma_colors <- viridis(5, option = "plasma")

#####load data!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!
#Results M1,2 and 3 intervention program
KF_DF<-read.csv("KEYFIGURES_DC_VETENHANCE_DEF_V4.csv")

#Basic characteristics of participants
VET_DF<-read.csv("VETERINARIANS_DC_VETENHANCE_V2.csv")

#Adding necessary covariates GENDER, GROUP,VETPRAC, GRADYEAR
KF_DF<-merge(KF_DF, VET_DF[,c(1:13)],by="VETERINARIAN")
#Set numeric
KF_DF$KG1<-as.numeric(KF_DF$KG1)
KF_DF$REPORTS_2C_AMR<-as.numeric(KF_DF$REPORTS_2C_AMR)
KF_DF$DENOMINATOR_KG5<-as.numeric(KF_DF$DENOMINATOR_KG5)

#transforming DDD to be normally distributed, see function above
KF_DF$ln_DDD<-lnn(KF_DF$DDD)

#creating a wide dataframe for each timepoint to observe differences
Regr_mean<-reshape(KF_DF[,c(1:3,which(colnames(KF_DF=="GROUP"),
which(colnames(KF_DF=="ln_DDD")))],
idvar = c("FARM","VETERINARIAN","GROUP"), timevar = "MEASURE", direction = "wide")

Regr_mean<-Regr_mean[,c(1:3,6,4,5)]
Regr_mean$diff_1_0<-Regr_mean$ln_DDD.1-Regr_mean$ln_DDD.0
Regr_mean$diff_2_0<-Regr_mean$ln_DDD.2-Regr_mean$ln_DDD.0
Regr_mean$diff_2_1<-Regr_mean$ln_DDD.2-Regr_mean$ln_DDD.1

Regr_mean$diffPrc_1_0<-(Regr_mean$ln_DDD.1-Regr_mean$ln_DDD.0)/Regr_mean$ln_DDD.0
Regr_mean$diffPrc_2_0<-(Regr_mean$ln_DDD.2-Regr_mean$ln_DDD.0)/Regr_mean$ln_DDD.0
#Regr_mean$diffPrc_2_1<-(Regr_mean$ln_DDD.2-Regr_mean$ln_DDD.1)/Regr_mean$ln_DDD.1
Regr_mean[which(Regr_mean$diffPrc_2_1==Inf),"diffPrc_2_1"]<-NA

#just adding the variables created above in the long format
KF_DF<-merge(KF_DF, Regr_mean[,c(2,4:length(Regr_mean))],by="FARM")

KF_DF$DiffALL<-ifelse(KF_DF$MEASURE==0,0,
  ifelse(KF_DF$MEASURE==1,KF_DF$diff_1_0,
  ifelse(KF_DF$MEASURE==2,KF_DF$diff_2_0,99999999)))

KF_DF$DiffPrcALL<-ifelse(KF_DF$MEASURE==0,0,
  ifelse(KF_DF$MEASURE==1,KF_DF$diffPrc_1_0,
  ifelse(KF_DF$MEASURE==2,KF_DF$diffPrc_2_0,99999999)))

#Making histogram and plot
hist(KF_DF$DDD,breaks=150)
hist(KF_DF$ln_DDD,breaks=150)

aggr_farm<-aggregate(KF_DF$ln_DDD, by=list(KF_DF$FARM), sum)
aggr_farm<-aggr_farm[order(aggr_farm[,2],decreasing=T),]

ggplot(data=KF_DF,aes(x=factor(FARM,levels=aggr_farm$Group.1),y=ln_DDD,fill=factor(MEASURE,levels=c(0:2))))+
  geom_col(position="dodge")+ theme(axis.text.x = element_text(angle = 90,size=6, vjust = 0.5,
hjust=1),legend.position="bottom")+
  guides(fill=guide_legend(title="Meeting"))+xlab("Farms_ID")

#clean data: we see some obs have only one value thus we exclude those
KF_DF<-KF_DF[-which(KF_DF$FARM %in% c(names(which(table(KF_DF$FARM)==1))))],]

#Power analysis
library(simr)

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store_power<-NULL
for ( i in c( -0.2843569,-0.3380281,-0.6810839)){
  model_pow<-lmer(ln_DDD ~ MEASURE + (MEASURE|GROUP/VETERINARIAN/FARM) ,
  data=KF_DF,control=lmerControl(optimizer="bobyqa"),REML = T)

  current_effects <- fixef(model_pow)
  print(current_effects)
  current_effects["MEASURE"] <- i
  print(current_effects)
  new_model_pow <- makeLmer(formula=ln_DDD ~ MEASURE + (MEASURE|GROUP/VETERINARIAN/FARM) ,
  fixef = current_effects,
  VarCorr = VarCorr(model_pow), # Retaining the random effects structure
  sigma = sigma(model_pow),
  data = KF_DF)

  power_result <- powerSim(new_model_pow,
  # test=fixed("factor(MEASURE)2"),
  nsim=2,progress=T)

  power_info<-data.frame(summary(power_result))

  store_power<-rbind(store_power,power_info)
}
load("store_power.Rdata") #your results
#save(store_power,file="store_power.Rdata")

#!!!!!!!!!!!! Figure 3 descriptive data DDDA ln !!!!!!!!!!!!!!!!!!!!!

#BOXPLOT farm level descriptives in ln
boxplot_fig3 <- ggplot() +
  geom_boxplot(data = KF_DF, aes(x = factor(GROUP), y = ln_DDD, fill = factor(MEASURE)), position = "dodge") +
  geom_point() +
  labs(
    title = "Antimicrobial use farms",
    x = "Groups",
    y = expression(DDDA[F]~"in ln")
  ) +
  guides(fill = guide_legend(title = "Measurement")) +
  scale_fill_manual(values = c("#F0F921FF", "#F89441FF", "#CC4678FF"))+
  theme(text = element_text(size = 16))

#saving figure
ggsave("Figure 3.eps", plot = boxplot_fig3, width = 10, height = 8, dpi = 900)

#!!!!!!!!!!!!checking seasonal effects!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!
KF_DF$Year<-ifelse((KF_DF$MEASURE==0 & KF_DF$GROUP==2),2,
  ifelse((KF_DF$MEASURE==1 & KF_DF$GROUP==2),2,
  ifelse((KF_DF$MEASURE==0 & KF_DF$GROUP==6),2,
  ifelse((KF_DF$MEASURE==0 & KF_DF$GROUP==1),1,
  ifelse((KF_DF$MEASURE==1 & KF_DF$GROUP==6),1,
  ifelse((KF_DF$MEASURE==1 & KF_DF$GROUP==1),1,
  ifelse((KF_DF$MEASURE==0 & KF_DF$GROUP==3),1,
  ifelse((KF_DF$MEASURE==2 & KF_DF$GROUP==2),1,
  ifelse((KF_DF$MEASURE==1 & KF_DF$GROUP==3),1,
  ifelse((KF_DF$MEASURE==0 & KF_DF$GROUP==4),1,
  ifelse((KF_DF$MEASURE==2 & KF_DF$GROUP==6),1,
  ifelse((KF_DF$MEASURE==1 & KF_DF$GROUP==4),1,
  ifelse((KF_DF$MEASURE==0 & KF_DF$GROUP==5),1,
  ifelse((KF_DF$MEASURE==2 & KF_DF$GROUP==1),1,
  ifelse((KF_DF$MEASURE==2 & KF_DF$GROUP==3),1,
  ifelse((KF_DF$MEASURE==1 & KF_DF$GROUP==5),1,
  ifelse((KF_DF$MEASURE==2 & KF_DF$GROUP==4),0,
  ifelse((KF_DF$MEASURE==2 & KF_DF$GROUP==5),0,99999)))))))))))))))))

KF_DF$Month<-ifelse((KF_DF$MEASURE==0 & KF_DF$GROUP==2),"Sept",
  ifelse((KF_DF$MEASURE==1 & KF_DF$GROUP==2),"Oct",
  ifelse((KF_DF$MEASURE==0 & KF_DF$GROUP==6),"Nov",
  ifelse((KF_DF$MEASURE==0 & KF_DF$GROUP==1),"Jan",
  ifelse((KF_DF$MEASURE==1 & KF_DF$GROUP==6),"Jan",
  ifelse((KF_DF$MEASURE==1 & KF_DF$GROUP==1),"Mar",
  ifelse((KF_DF$MEASURE==0 & KF_DF$GROUP==3),"Mar",
  ifelse((KF_DF$MEASURE==2 & KF_DF$GROUP==2),"Apr",
  ifelse((KF_DF$MEASURE==1 & KF_DF$GROUP==3),"May",
  ifelse((KF_DF$MEASURE==0 & KF_DF$GROUP==4),"Jun",
  ifelse((KF_DF$MEASURE==2 & KF_DF$GROUP==6),"Jul",
  ifelse((KF_DF$MEASURE==1 & KF_DF$GROUP==4),"Aug",
  ifelse((KF_DF$MEASURE==0 & KF_DF$GROUP==5),"Sept",
  ifelse((KF_DF$MEASURE==2 & KF_DF$GROUP==1),"Oct",
  ifelse((KF_DF$MEASURE==2 & KF_DF$GROUP==3),"Nov",
  ifelse((KF_DF$MEASURE==1 & KF_DF$GROUP==5),"Nov",
  ifelse((KF_DF$MEASURE==2 & KF_DF$GROUP==4),"Mar",
  ifelse((KF_DF$MEASURE==2 & KF_DF$GROUP==5),"Jun",99999)))))))))))))))))

KF_DF$Season<-ifelse(KF_DF$Month %in%c("Jun","Jul","Aug"),"Heat",
  ifelse(KF_DF$Month %in%c("Sept","Oct","Nov","Jan","Mar"),"Cold","nothing"))

KF_DF$Season<-factor(KF_DF$Season, levels=c("nothing","Cold","Heat"))

#also checked it as 6-month effect and got same results
#with this model we check if year variable the secular effect is present and there is none thus we can exclude it

#model_sec<-lmer(ln_DDD ~ factor(MEASURE) + (Season) +
#(MEASURE|GROUP/VETERINARIAN/FARM) , data=KF_DF,
#control=lmerControl(optimizer="bobyqa"),
#REML = T)

#AIC(model_sec)

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#summary(model_sec)

#!!!!!!!!!!!!!!Check for RTM effect!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!
# If cor between t0 and t1 is <1 then there is RTM
#Cor t0,t1
cor.test(Regr_mean$ln_DDD.0,Regr_mean$ln_DDD.1)

#cor t0,t2
cor.test(Regr_mean$ln_DDD.0,Regr_mean$ln_DDD.2)

#dif-0-1-2
model_dif_1<-lmer(diff_1_0 ~ln_DDD.0 + (ln_DDD.0|GROUP/VETERINARIAN) ,
data=Regr_mean,control=lmerControl(optimizer="bobyqa"),REML = T)
model_dif_2<-lmer(diff_2_0 ~ln_DDD.0 + (ln_DDD.0|GROUP/VETERINARIAN) ,
data=Regr_mean,control=lmerControl(optimizer="bobyqa"),REML = T)

#difPrC-0-1-2
model_difPrC_1<-lmer(diffPrC_1_0 ~ln_DDD.0 + (ln_DDD.0|GROUP/VETERINARIAN) ,
data=Regr_mean,control=lmerControl(optimizer="bobyqa"),REML = T)
model_difPrC_2<-lmer(diffPrC_2_0 ~ln_DDD.0 + (ln_DDD.0|GROUP/VETERINARIAN) ,
data=Regr_mean,control=lmerControl(optimizer="bobyqa"),REML = T)

Regr_mean$fit_dif_1<-(predict(model_dif_1,Regr_mean,allow.new.levels=T,re.form=NA))
Regr_mean$fit_dif_2<-(predict(model_dif_2,Regr_mean,allow.new.levels=T,re.form=NA))

Regr_mean$fit_difPrC_1<-(predict(model_difPrC_1,Regr_mean,allow.new.levels=T,re.form=NA))
Regr_mean$fit_difPrC_2<-(predict(model_difPrC_2,Regr_mean,allow.new.levels=T,re.form=NA))

ggplot() +
  geom_point(data=Regr_mean, aes(x=(ln_DDD.0), y=(diffPrC_1_0)),col="dark green")+
  geom_line(data=Regr_mean, aes(x=(ln_DDD.0), y=fit_difPrC_1),col="dark green")+
  #geom_point(data=Regr_mean, aes(x=(ln_DDD.1), y=(diffPrC_2_1)),col="blue")+
  #geom_line(data=Regr_mean, aes(x=(ln_DDD.1), y=fit_difPrC_3),col="red")+
  #geom_point(data=Regr_mean, aes(x=(ln_DDD.0), y=(diffPrC_2_0)),col="red")+
  #geom_line(data=Regr_mean, aes(x=(ln_DDD.0), y=fit_difPrC_2),col="red")+
  #geom_line(aes(x=(0:9), y=0:-9),col="black")+
  geom_hline(yintercept =0, color="black",size=1,linetype="dotted")+
  geom_hline(yintercept =-1, color="purple",size=1,linetype="dotted")#+
  #scale_y_continuous(sec.axis = sec_axis(~., name = "diffPrC_2_0"))

# Normal model
model<-lmer(ln_DDD ~ factor(MEASURE) + (MEASURE|GROUP/VETERINARIAN/FARM) ,
data=KF_DF,control=lmerControl(optimizer="bobyqa"),REML = T)
summary(model)

#check if the non extrapolated version of ddd differs
KF_DF$DDD_nonextrapol<-#KF_DF$DDD/2
ifelse(KF_DF$MEASURE!=0,KF_DF$DDD/2,KF_DF$DDD)

for(i in unique(KF_DF$FARM)){
  trfv<-KF_DF[which(KF_DF$FARM==i),]
  KF_DF$DDD_nonextrapol[which(KF_DF$FARM==i & KF_DF$MEASURE==2)] <-
trfv$DDD_nonextrapol[which(trfv$MEASURE==1)]+trfv$DDD_nonextrapol[which(trfv$MEASURE==2)]
KF_DF$DDD_nonextrapol[which(KF_DF$FARM==i & KF_DF$MEASURE==1)] <- NA
}

#AIC(model)
KF_DF_extrp<-KF_DF[-which(KF_DF$MEASURE==1),]
KF_DF_extrp$ln_DDD_nonextrapol<-lrm(KF_DF_extrp$DDD_nonextrapol)
KF_DF_extrp$MEASURE<-ifelse(KF_DF_extrp$MEASURE==2,1,KF_DF_extrp$MEASURE)

model_extrp<-lmer(ln_DDD_nonextrapol ~ (MEASURE) + (1|GROUP/VETERINARIAN/FARM) ,
data=KF_DF_extrp,control=lmerControl(optimizer="bobyqa"),REML = T)
summary(model_extrp)

1-exp(coef(summary(model_extrp))[-1,1])

ggplot()+
  geom_boxplot(data=KF_DF_extrp,aes(x=factor(GROUP),y=(ln_DDD_nonextrapol), fill=factor(MEASURE)),position = "dodge")

ggplot()+
  geom_boxplot(data=KF_DF_extrp,aes(x=factor(GROUP),y=(ln_DDD), fill=factor(MEASURE)),position = "dodge")

# Adjusting for RTM effect in regression by using baseline as predictor and mean centering it

model_RTM<-lmer(ln_DDD ~ I(ln_DDD.0-mean(ln_DDD.0)) +factor(MEASURE) +
(1|GROUP/VETERINARIAN/FARM) , data=KF_DF[-
which(KF_DF$MEASURE==0),],control=lmerControl(optimizer="bobyqa"),REML = T)

summary(model_RTM)
#AIC(model_RTM)

# So the effect of meeting from t1 to t2 is equivalent thus the RTM although it is present for a few observations it doesn't
effect the estimates
1-exp(coef(summary(model)) [3,1]-coef(summary(model)) [2,1])
1-exp(coef(summary(model_RTM)) [3,1])
ggplot(Regr_mean, aes(x=ln_DDD.0)) + geom_histogram(binwidth=0.1)+
  geom_vline(xintercept = c((mean(Regr_mean$ln_DDD.0,na.rm=T) + c(-1.5, 1.5) * sd(Regr_mean$ln_DDD.0,na.rm=T))),
linetype="dotted", color = "blue", size=1.5)

#!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!! Final effect on DDD!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!

#!!!!!!!!!!!!!! Figure 3 and 4 and table results per group !!!!!!!!!!!!!!!!!!!!!!!

# So the % decrease due to the effect of the meeting is approximatly
model<-lmer(ln_DDD ~ factor(MEASURE) + (MEASURE|GROUP/VETERINARIAN/FARM) ,
data=KF_DF,control=lmerControl(optimizer="bobyqa"),REML = T)
summary(model)

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CI_model<-confint(model, method="Wald", level=1-0.05/2)
1-exp(coef(summary(model))[-1,1])
1-exp(CI_model[(nrow(CI_model)-1):nrow(CI_model),])

#bonferroni adjustment/8: 6 groups, meeting1 and meeting2
Random_DF<-data.frame(broom.mixed::tidy(model, effects = "ran_vals", conf.int = TRUE, conf.level = (1-(0.05/8)) ))

Random_DF_Group<-Random_DF[which(Random_DF$group=="GROUP" & Random_DF$term=="MEASURE"),]

Random_DF_Group$exp_coef_1<-1-exp( coef(summary(model))[2,1] + Random_DF_Group$estimate)
Random_DF_Group$exp_CIlow_1<-1-exp(coef(summary(model))[2,1] +Random_DF_Group$conf.low)
Random_DF_Group$exp_CIhigh_1<-1-exp(coef(summary(model))[2,1] +Random_DF_Group$conf.high)

Random_DF_Group$exp_coef_2<-1-exp( coef(summary(model))[3,1] + Random_DF_Group$estimate)
Random_DF_Group$exp_CIlow_2<-1-exp(coef(summary(model))[3,1] +Random_DF_Group$conf.low)
Random_DF_Group$exp_CIhigh_2<-1-exp(coef(summary(model))[3,1] +Random_DF_Group$conf.high)

round.off(Random_DF_Group$exp_coef_1,2)
apply(Random_DF_Group[,c(9:14)],2,FUN=round.off)

dfg<-data.frame(coef=c(1-exp(coef(summary(model))[-1,1])),
               upper=(1-exp(CI_model[(nrow(CI_model)-1):nrow(CI_model),)])[,2],
               lower=(1-exp(CI_model[(nrow(CI_model)-1):nrow(CI_model),)])[,1])
dfg$var<-c("M1", "M2")

AMUf<-ggplot(dfg, aes(var, coef*100)) +
  geom_hline(yintercept=0, lty=3, lwd=1, colour="grey50") +
  geom_errorbar(aes(ymin=lower*100, ymax=upper*100), lwd=2,width=0 ) +coord_flip()+
  geom_point(size=4)+
  ylim(0, 100)+
  scale_linetype_manual(values=c(2,1))+
  labs(x="",y="% Reduction antimicrobial use farms")+
  theme(legend.position="right",panel.background = element_rect(fill = 'white'),
        legend.key.width = unit(2, 'cm'),
        legend.text = element_text(face="bold", size=15),
        legend.title = element_text(face="bold", size=15),
        axis.text.x=element_text(angle=0,hjust=0.3,vjust=1,face="bold", size=15),
        axis.text.y=element_text(face="bold", size=15),
        axis.title.y = element_text(vjust=2,face="bold", size=15),
        axis.title.x = element_text(vjust=0,face="bold", size=15),
        panel.grid = element_line(colour = "#e3e3e3"))

#saving figure
ggsave("Figure 4.eps", plot = AMUf, width = 10, height = 4, dpi = 900)

##### PERFORMANCE INDICATORS #####

#####load data#####
#loading again the data and some cleaning them from the beginning
#because some obs don't need to be removed as before
#Results M1,2 and 3 intervention program
KF_DF<-read.csv("KEYFIGURES_DC_VETENHANCE_DEF_V4.csv")
#Basic characteristics of participants
VET_DF<-read.csv("VETERINARIANS_DC_VETENHANCE_V2.csv")

#Adding necessary covariates GENDER, GROUP,VETPRAC, GRADYEAR
KF_DF<-merge(KF_DF, VET_DF[,c(1:13)],by="VETERINARIAN")
#Set numeric
KF_DF$KG1<-as.numeric(KF_DF$KG1)
KF_DF$REPORTS_2C_AMR<-as.numeric(KF_DF$REPORTS_2C_AMR)
KF_DF$DENOMINATOR_KG5<-as.numeric(KF_DF$DENOMINATOR_KG5)
KF_DF$KG3<-as.numeric(KF_DF$KG3)

#transforming DDD to be normally distributed
KF_DF$ln_DDD<-lnn(KF_DF$DDD)

#####Making new dataframe with data for performance indicators #####
Vet_Aggr <- aggregate(list(KF_DF$DDD,
                           KF_DF$KG1,
                           KF_DF$NUMERATOR_KG2,
                           KF_DF$KG3,KF_DF$REPORTS_2C_AMR,
                           KF_DF$DENOMINATOR_KG5),
                      by=list(KF_DF$VETERINARIAN,
                              KF_DF$MEASURE,KF_DF$GROUP), sum)

#give names to new data set Vet_Aggr
names(Vet_Aggr)<-c("VETERINARIAN", "MEASURE", "GROUP", "DDD", "KG1", "NUMERATOR_KG2", "KG3", "REPORTS_2C_AMR", "DENOMINATOR_KG5")

#merge with data of veterinarians
Vet_Aggr<-merge(Vet_Aggr, VET_DF[,c(1,11:13)],by="VETERINARIAN")

#set numeric/ factor
Vet_Aggr<-Vet_Aggr[-which(Vet_Aggr$VETERINARIAN %in%as.numeric(names(which(table(Vet_Aggr$VETERINARIAN)==1))))],]
Vet_Aggr$MEASURE<-factor(Vet_Aggr$MEASURE)

##### Figure 5 and additional files #####

#Formula PI Antimicrobial use veterinarians
Vet_Aggr$KF4_VET<-ifelse(Vet_Aggr$MEASURE==0,
                        Vet_Aggr$DDD/Vet_Aggr$FARMSVET.ENHANCE_0/20,
                        ifelse(Vet_Aggr$MEASURE==1,
                              Vet_Aggr$DDD/Vet_Aggr$FARMSVET.ENHANCE_1/20,
                              ifelse(Vet_Aggr$MEASURE==2,
                                    Vet_Aggr$DDD/Vet_Aggr$FARMSVET.ENHANCE_2/20,9999)))

#BOXPLOT

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boxplot_fig5<-ggplot()+
  geom_boxplot(data=Vet_Aggr,aes(x=factor(GROUP),y=(KF4_VET),
                                fill=factor(MEASURE)),position = "dodge")+
  labs(title = "Antimicrobial use veterinarians",x="Groups",y="PI Antimicrobial use")+
  labs(fill="Measurement")+
  scale_fill_manual(values = c("#F0F921FF", "#F89441FF", "#CC4678FF")) +
  theme(text = element_text(size = 16))

#saving figure
ggsave("Figure 5.eps", plot = boxplot_fig5, width = 10, height = 8, dpi = 900)

#model PI Antimicrobials
Vet_Aggr_44<-Vet_Aggr[,which(colnames(Vet_Aggr) %in%c("KF4_VET", "MEASURE","GROUP","VETERINARIAN"))]
model_Aggr_KF4<- gamlss(KF4_VET ~ (MEASURE)+re(random = ~ 1 | GROUP/VETERINARIAN, method = "REML"), family = GA, data
=Vet_Aggr_44)

# Obtain confidence intervals for model coefficients
ci_model_Aggr_KF4 <- confint(model_Aggr_KF4)
coef(model_Aggr_KF4)

KF4_DF<-data.frame(coef=c(1-data.frame(exp(coef(model_Aggr_KF4)))[c(2,3),1]),
                    upper=1-(exp(data.frame(confint(model_Aggr_KF4, level=1-0.05/2))[c(2,3),c(1,2)]))[,2],
                    lower=1-(exp(data.frame(confint(model_Aggr_KF4, level=1-0.05/2))[c(2,3),c(1,2)]))[,1])
KF4_DF$var<-c("M1","M2")

KF4_DF<-KF4_DF[,c(4,1,3,2)]

#Additional file 3
ANALYSES_PIAMU<-ggplot(KF4_DF, aes(var, coef*100)) +
  geom_hline(yintercept=0, lty=3, lwd=1, colour="grey50") +
  geom_errorbar(aes(ymin=lower*100, ymax=upper*100), lwd=2,width=0 ) +coord_flip()+
  geom_point(size=4)+
  scale_linetype_manual(values=c(2,1))+
  labs(x="",y="% reduction PI antimicrobial use")+
  theme(legend.position="right",panel.background = element_rect(fill = 'white'),
        legend.key.width = unit(2, 'cm'),
        legend.text = element_text(face="bold", size=15),
        legend.title = element_text(face="bold", size=15),
        axis.text.x=element_text(angle=0,hjust=0.3,vjust=1,face="bold", size=15),
        axis.text.y=element_text(face="bold", size=15),
        axis.title.y = element_text(vjust=2,face="bold", size=15),
        axis.title.x = element_text(vjust=0,face="bold", size=15),
        panel.grid = element_line(colour = "#e3e3e3"))

#saving figure
ggsave("Additional File 3.eps", plot = ANALYSES_PIAMU, width = 10, height = 4, dpi = 900)

#!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!
#Formula PI Ratio of 1"st" * " to 2"nd" * " or 3"rd" * " choice antimicrobials
Vet_Aggr$KF2_VET<-Vet_Aggr$NUMERATOR_KG2/Vet_Aggr$DDD/100

#making dataframe for plot
Vet_AggrK22<-Vet_Aggr[,which(colnames(Vet_Aggr) %in%c("KF2_VET", "MEASURE","GROUP","VETERINARIAN"))]

#BOXPLOT figure 7
boxplot_fig7 <- ggplot() +
  geom_boxplot(data = Vet_Aggr, aes(x = factor(GROUP), y = (KF2_VET), fill = factor(MEASURE)), position = "dodge") +
  labs(
    title = expression("Ratio of 1"st" * " to 2"nd" * " or 3"rd" * " choice antimicrobials"),
    x = "Groups",
    y = expression("PI Ratio of 1"st" * " to 2"nd" * " or 3"rd" * " choice antimicrobials")
  ) +
  labs(fill = "Measurement") +
  scale_fill_manual(values = c("#F0F921FF", "#F89441FF", "#CC4678FF")) +
  theme(text = element_text(size = 16))

#saving figure
ggsave("Figure 6.eps", plot = boxplot_fig7, width = 10, height = 8, dpi = 900)

#Model PI 1"st" * " to 2"nd" * " or 3"rd" * " choice antimicrobials
model_Aggr_KF2<- gamlss(KF2_VET ~ (MEASURE)+re(random = ~ 1 | GROUP/VETERINARIAN, method = "REML"), family = BEINF, data
=Vet_AggrK22)

FIG_2_DF<-data.frame(coef=c(data.frame(exp(coef(model_Aggr_KF2)))[c(2,3),1]),
                    upper=(exp(data.frame(confint(model_Aggr_KF2, level=1-0.05/2))[c(2,3),c(1,2)]))[,2],
                    lower=(exp(data.frame(confint(model_Aggr_KF2, level=1-0.05/2))[c(2,3),c(1,2)]))[,1])
FIG_2_DF$var<-c("M1","M2")

FIG_2_DF<-FIG_2_DF[,c(4,1,3,2)]

#Additional file 4
ANALYSE_RAT<-ggplot(FIG_2_DF, aes(var, coef)) +
  geom_hline(yintercept=1, lty=3, lwd=1, colour="grey50") +
  geom_errorbar(aes(ymin=lower, ymax=upper), lwd=2,width=0 ) +coord_flip()+
  geom_point(size=4)+
  #ylim(0, 100)+
  scale_linetype_manual(values=c(2,1))+
  labs(x="",y=expression("Relative proportion ratio PI 1"st" * " to 2"nd" * " or 3"rd" * " choice antimicrobials"))
  )+
  theme(legend.position="right",panel.background = element_rect(fill = 'white'),
        legend.key.width = unit(2, 'cm'),
        legend.text = element_text(face="bold", size=15),
        legend.title = element_text(face="bold", size=15),
        axis.text.x=element_text(angle=0,hjust=0.3,vjust=1,face="bold", size=15),
        axis.text.y=element_text(face="bold", size=15),
        axis.title.y = element_text(vjust=2,face="bold", size=15),
        axis.title.x = element_text(vjust=0,face="bold", size=15),

```

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panel.grid = element_line(colour = "#e3e3e3"))

#saving figure
ggsave("Additional File 4.eps", plot = ANALYSE_RAT, width = 10, height = 4, dpi = 900)

#!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!! Figure 7 and Additional Files !!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!

#Formule PI Argumentation for 2"nd" * " choice antimicrobials
Vet_Aggr$KF5_VET<-Vet_Aggr$REPORTS_2C_AMR/Vet_Aggr$DENOMINATOR_KG5

Vet_AggrK5<-Vet_Aggr[-which(Vet_Aggr$VETERINARIAN %in%
c(unique(Vet_Aggr$VETERINARIAN[which(is.na(Vet_Aggr$KF5_VET))]),as.numeric(names(which(table(Vet_Aggr$VETERINARIAN)==1))))),]

#BOXPLOT
boxplotPI5<-ggplot()+ geom_boxplot(data=Vet_Aggr,aes(x=factor(GROUP),y=(KF5_VET), fill=factor(MEASURE)),position =
"dodge")+labs(title = expression("Argumentation for 2"nd"*"choice antimicrobials"),

x="Groups",y=expression("PI Argumentation for 2"nd" * " choice
antimicrobials"))+labs(fill="Measurement")+scale_fill_manual(values = c("#F0F921FF", "#F89441FF", "#CC4678FF"))+
theme(text = element_text(size = 16))

#saving figure
ggsave("Figure 7.eps", plot = boxplotPI5, width = 10, height = 8, dpi = 900)

#dataframe for plot PI Argumentation for 2"nd" * " choice antimicrobials
Vet_AggrK55<-Vet_AggrK5[,which(colnames(Vet_AggrK5) %in%c("KF5_VET", "MEASURE", "GROUP", "VETERINARIAN"))]

#model PI Argumentation for 2"nd" * " choice antimicrobials
model_Aggr_KF5<-gamlss(KF5_VET ~ factor(MEASURE)+re(random = ~ 1 | GROUP/VETERINARIAN, method = "REML"), family = BEINF,
data =Vet_AggrK55)

FIG_5_DF<-data.frame(coef=c(data.frame(exp(coef(model_Aggr_KF5)))[c(2,3),1]),
upper=(exp(data.frame(confint(model_Aggr_KF5, level=1-0.05/2))[c(2,3),c(1,2)]))[,2],
lower=(exp(data.frame(confint(model_Aggr_KF5, level=1-0.05/2))[c(2,3),c(1,2)]))[,1])
FIG_5_DF$var<-c("M1", "M2")

FIG_5_DF<-FIG_5_DF[,c(4,1,3,2)]

#Additional file 5
ANALYSES_PIARG<-ggplot(FIG_5_DF, aes(var, coef)) +
geom_hline(yintercept=1, lty=3, lwd=1, colour="grey50") +
geom_errorbar(aes(ymin=lower, ymax=upper), lwd=2,width=0 ) +coord_flip()+
geom_point(size=4)+
#ylim(0, 100)+
scale_linetype_manual(values=c(2,1))+
labs(x="",y=expression("Relative proportion ratio PI argumentation for 2"nd" * " choice"))+
theme(legend.position="right",panel.background = element_rect(fill = 'white'),
legend.key.width = unit(2, 'cm'),
legend.text = element_text(face="bold", size=15),
legend.title = element_text(face="bold", size=15),
axis.text.x=element_text(angle=0,hjust=0.3,vjust=1,face="bold", size=15),
axis.text.y=element_text(face="bold", size=15),
axis.title.y = element_text(vjust=2,face="bold", size=15),
axis.title.x = element_text(vjust=0,face="bold", size=15),
panel.grid = element_line(colour = "#e3e3e3"))

#saving figure
ggsave("Additional File 5.eps", plot = ANALYSES_PIARG, width = 10, height = 4, dpi = 900)

#!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!Figure 8 and Additional Files!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!

#Formula PI Bacteriological examination
Vet_Aggr$KF1_VET<-ifelse(Vet_Aggr$MEASURE==0,
Vet_Aggr$KG1/Vet_Aggr$FARMSVET.ENHANCE_0,
ifelse(Vet_Aggr$MEASURE==1,
Vet_Aggr$KG1/Vet_Aggr$FARMSVET.ENHANCE_1,
ifelse(Vet_Aggr$MEASURE==2,
Vet_Aggr$KG1/Vet_Aggr$FARMSVET.ENHANCE_2,9999)))

#removing NA's
Vet_AggrK1<-Vet_Aggr[-which(Vet_Aggr$VETERINARIAN %in%
unique(Vet_Aggr$VETERINARIAN[which(is.na(Vet_Aggr$KF1_VET))]),)]

#making dataframe for plot
Vet_AggrK11<-Vet_AggrK1[,which(colnames(Vet_AggrK1) %in%c("KF1_VET", "MEASURE", "GROUP", "VETERINARIAN"))]

#BOXPLOT figure 11
boxplot_fig11<-ggplot()+
geom_boxplot(data=Vet_AggrK11,aes(x=factor(GROUP),y=(KF1_VET), fill=factor(MEASURE)),position = "dodge")+
labs(title = "Bacteriological examination",x="Groups",y="PI Bacteriological examination", fill="Measurement")+
scale_fill_manual(values = c("#F0F921FF", "#F89441FF", "#CC4678FF"))+
theme(text = element_text(size = 16))

#saving figure
ggsave("Figure 8.eps", plot = boxplot_fig11, width = 10, height = 8, dpi = 900)

#model PI Bacteriological examination
model_Aggr_KF1<-gamlss(KF1_VET ~ (MEASURE)+re(random = ~ 1|GROUP/VETERINARIAN, method = "REML"), family = BEINF, data
=Vet_AggrK11)
print(data.frame(exp(coef(model_Aggr_KF1)))[c(2,3),1])
exp(data.frame(confint(model_Aggr_KF1))[c(2,3),c(1,2)])

FIG_1_DF<-data.frame(coef=c(data.frame(exp(coef(model_Aggr_KF1)))[c(2,3),1]),
upper=(exp(data.frame(confint(model_Aggr_KF1, level=1-0.05/2))[c(2,3),c(1,2)]))[,2],
lower=(exp(data.frame(confint(model_Aggr_KF1, level=1-0.05/2))[c(2,3),c(1,2)]))[,1])
FIG_1_DF$var<-c("M1", "M2")

```



```

#so participants with a DDDA lower dan 20 score the maximum score of 1
Vet_AggrTotaalMAX1 <- Vet_AggrTotaal %>%
  mutate(KF4_VET = pmin(1, pmax(0, KF4_VET)))

#remove NA's
Vet_AggrTotaal <- na.omit(Vet_AggrTotaal)

#Giving colums new names
huidige_namen <- c("KF1_VET", "KF2_VET", "KF3_VET", "KF4_VET", "KF5_VET")
nieuwe_namen <- c("Bacteriological examination", "Ratio of 1st to 2nd or 3rd choice antimicrobials", "Corticosteroids",
"Antimicrobial use", "Argumentation for 2nd choice antimicrobials")
Vet_AggrTotaalMAX2 <- Vet_AggrTotaalMAX1 %>%
  rename_at(vars(huidige_namen), ~nieuwe_namen)

#making dataframe for plot
Vet_AggrTotaalMAX2_LONG <- Vet_AggrTotaalMAX2 %>%
  gather(Variable, Value, "Antimicrobial use", "Ratio of 1st to 2nd or 3rd choice antimicrobials", "Argumentation for 2nd
choice antimicrobials", "Bacteriological examination", "Corticosteroids")

# Removing NA's
Vet_AggrTotaalMAX2_LONG <- Vet_AggrTotaalMAX2_LONG %>%
  filter(!is.na(Value))

#Desired order in plot
gewenste_volgorde <- c("Antimicrobial use",
"Ratio of 1st to 2nd or 3rd choice antimicrobials",
"Argumentation for 2nd choice antimicrobials",
"Bacteriological examination",
"Corticosteroids")

#Preparation plot figure 15
totaal_per_variabele <- Vet_AggrTotaalMAX2_LONG %>%
  filter(Variable %in% gewenste_volgorde) %>%
  group_by(Variable) %>%
  summarise(total = sum(Value, na.rm = TRUE))

# desired order labels
gewenste_labels <- totaal_per_variabele$Variable

# labels with superscript
gewenste_labels <- c(
"Antimicrobial use",
expression("Ratio of 1"^st * " to 2"^nd * " or 3"^rd * " choice antimicrobials"),
expression("Argumentation for 2"^nd * " choice antimicrobials"),
"Bacteriological examination",
"Corticosteroids")

# set in factor
Vet_AggrTotaalMAX2_LONG$Variable <- factor(Vet_AggrTotaalMAX2_LONG$Variable, levels = gewenste_volgorde)

#making plot figure 15
gestapeld_kleur <- ggplot(Vet_AggrTotaalMAX2_LONG, aes(x = factor(MEASURE), y = Value, fill = Variable)) +
  geom_bar(stat = "identity", position = "fill", color = "NA") +
  labs(
x = "Measurement",
y = expression("Distribution performance indicators"),
fill = NULL,
title = expression("Combined results all participants")
) +
scale_fill_manual(
values = plasma_colors,
labels = gewenste_labels
) +
theme_minimal() +
theme(
plot.background = element_rect(fill = "white"),
legend.title = element_blank()
) +
scale_y_continuous(labels = scales::label_parse())

plot(gestapeld_kleur)

#saving figure
ggsave("Additional File 8.jpg", plot = gestapeld_kleur, width = 10, height = 8, dpi = 900)

# Set the factor levels for the Variable column
Vet_AggrTotaalMAX2_LONG$Variable <- factor(Vet_AggrTotaalMAX2_LONG$Variable, levels = gewenste_volgorde)

# Scatter plot with jitter and custom labels
scatter_additional3 <- ggplot(Vet_AggrTotaalMAX2_LONG, aes(x = factor(MEASURE), y = Value, color = Variable)) +
  geom_point(position = position_jitterdodge(dodge.width = 0.8, jitter.width = 0.2), size = 3) +
  labs(
x = "Measurement",
y = "Performance indicators per participants",
color = NULL, # Remove the legend title
title = "Combined results all participants"
) +
scale_color_manual(
values = plasma_colors,
labels = gewenste_labels
) +
theme_minimal() +
theme(
plot.background = element_rect(fill = "white"),
legend.title = element_blank()
) +
guides(color = guide_legend(title = NULL))

```

```
# Plot the scatter plot
plot(scatter_additional3)

# Optional: Save the scatter plot
ggsave("Additional File 9_Scatter.eps", plot = scatter_additional3, width = 10, height = 8, dpi = 900)
```