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Deliverable D8.6

Pulmonar microbiome effects related to porcine influenza infections

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Table of contents

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1. Summary

Objectives:

The microbiome has proven to play an important role in shaping the local and systemic immunity. Whereas in pigs the role of the microbiome in the intestinal tract is well studied, its composition and changeability on mucosal surfaces of the lung is not or only poorly described, and its role during viral and bacterial infection as well as the impact of infections on the microbiome is largely unknown. The composition of the respiratory tract microbiome in the piglet is most likely determined by the microbiome of the sow, littermates and other pigs in the nursery unit and the effect on the host immunity in the respiratory tract are unknown. Other than planned in the Grant Agreement (and as suggested by the Deliverable title), the work presented here focused on host-pathogen-microbiome interactions in the context of (co-)infections with porcine reproductive and respiratory syndrome virus (PRRSV) and/or *Streptococcus suis* (*S. suis*), rather than swine influenza infection. The results of the work performed in WP8 Task 8.3 confirmed that a viral/bacterial co-infection (PRRSV/*S. suis)* and the bacterial infection (*S. suis)* alone can induce significant differences in the relative abundance of a total of 27 bacterial species compared to the control group. Furthermore, a *S. suis* infection induced a different microbiome composition when preceded by a PRRSV infection, compared to the *S. suis* infection alone. As expected, the microbiological background after birth – farm versus biosafety (level 2) containment – determined the composition of the bronchial lung microbiome in control pigs of each of the two groups and resulted in differences in the microbiome composition after PRRSV/*S. suis* co-infection and *S. suis* infection alone.

Rationale:

The complexity of the respiratory tract microbiome is known to play a role in immune training and is expected to be involved in additional important functions. The role of conventional housing on the composition of the microbiome of the respiratory tract, here especially on the endobronchial microbiome, was studied by comparing it with the microbiome established in pigs raised in semi-sterile conditions, which are born by caesarean-section (CDCD pigs). Next to this comparison, the study aimed to address the effects of a viral PRRSV infection on a combined or single *S. suis* infection on the

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composition of the respiratory microbiome. Additional immunological and pathological analyses were performed but are reported in deliverable D7.6.

Teams involved:

Wageningen Research/ Wageningen Bioveterinary Research

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2. Introduction

In the last decennia, microbiome research has been extensively performed and was mostly focussed on the gut microbiome. The relevance of the intestinal microbiome has been shown for the local mucosae, but also by system spread of bacterial metabolites on immunity, e.g. the lung system, known as the gut-lung axis. Whereas the gut microbiome has been well-studied, and changes/adaptation in the porcine gut microbiome have been shown to be caused by to age, husbandry and management, the microbiome on other mucosal surfaces is not or only poorly described, and the role in infection and impact of infections on the microbiome are largely unknown. The microbiome of the respiratory tract has to be distinguished into that of the upper respiratory tract, i.e. nasal microbiome, pharyngeal/tonsillar microbiome and that of the lower respiratory tract, i.e. the endobronchial microbiome and the microbiome in the alveolar space. It is generally accepted, that quantity and diversity of the respiratory microbiome is influenced by the ambient air microbiome and differs largely between upper and lower respiratory tract. Results from a recent study in pigs suggest that airborne bacteria make up the highest portion of the lung microbiome, especially the bronchi, but that bacterial communities differ between bronchi and alveolar space in pigs (1).

Interactions between the developing microbiome and maturing immune system in early life are critical for establishment of a homeostasis beneficial to both host and commensals. The lung harbours a diverse community of microbes associated with health and local or systemic disease. (2). The complexity of the respiratory tract microbiome is known to play a role in immune training and expected to be involved in additional important functions (3). A bidirectional relationship between the microbiome

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and host susceptibility and airway infection is assumed. It is reasonable to speculate that factors which influence the establishment of the early microbiome in neonates, such as gestational age, mode of birth, type of feeding, and antibiotic therapy, might also affect maturation and activity of the pulmonary antimicrobial immune defence (3). A recent study, for example, demonstrated that gestational age and other factors influenced microbiome diversification and pulmonary expression of IL-33 as well as genes linked with IgA production in human infants. The microbiome plays a crucial role in regulating both baseline immune activation and various infection-induced antimicrobial defence pathways after birth and throughout life. These findings are based on studies in mice, but the relevance of the respiratory microbiome has not yet been shown in pigs. In current pig farming practices piglets are born in farrowing units with several litters born at a time, which are exposed to a farm- and pig-specific, microbial ambient environment. The known higher susceptibility of animals, i.e. mice and pigs, born and raised in gnotobiotic or specific pathogen free conditions is considered to be related to a less competent immune system. The relation of the immune competence with the lack of exposition to maternal and pig-specific ambient microbiome is unclear and needs to be clarified.

Examples of bacterial pathogens that are associated with respiratory diseases in pigs, include, e.g. *Mycoplasma hyopneumoniae, Glaesseralla parasuis,* and *Actinobacillus pleuropneumoniae*. These pathogens may in turn be associated with a specific respiratory microbiome composition. Furthermore, changes in microbiome and microbiome related immune defence might result in a higher susceptibility to airway and systemic infections as can be seen with *Streptococcus suis* infections. Viral infections such as swine influenza or PRRSV have been shown to affect the

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microbiome in the upper respiratory tract in experimentally infected pigs (4) and might pave the way for successive bacterial infections.

In previous studies we have shown disease aggravation of a *Streptococcus suis* infection after a previous infection with Porcine Reproductive and Respiratory Syndrome Virus (PRRSV) type 1. PRRSV is known to infect macrophages and induces interstitial pneumonia, most of the times without clear clinical disease signs, but with effects on the susceptibility to bacterial infections. The virus infection might also impact the microbiome of the lungs and the resulting change of the lung microbiome might also contribute to an increased virulence of a *S. suis* infection. This study set out to investigate the relation of these pathogens in regard to the impact of the viral infection on the porcine respiratory microbiota.

In the description of work of the project, it was originally planned to study the relation and effect of swine influenza with and on the lung microbiome. During the project phase the European Animal Health law was established in the member states and PRRSV belongs to one of the listed diseases, whereas swine influenza is not. The legal and economic relevance of PRRSV infections have supported the decision to study the effect of PRRSV instead of swine influenza.

3. Results

Study design: A group of 24 conventional birth pigs and a group of 24 caesarean-derived colostrum-deprived pigs (CDCD) of 6 weeks of age deriving from the same breeding herd were used for this study. The conventional pigs were housed during the farrowing phase together with the mother sow on the farm of origin, whereas the CDCD pigs were born under sterile circumstances and then housed in in- and outlet air HEPA

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filtered animal rooms, which were decontaminated and controlled to be bacterial free at the day of birth. At five weeks of age, all pigs were housed under BSL2 conditions and the two groups, with a different microbiological background were subdivided into groups of 8 pigs, in order to study the effect of single or co-infection: (1) non-infected control group; (2) group infected with *Streptococcus suis* at day 14; and (3) group co-infected with PRRSV I at day 0 and *S. suis* serotype 2 at day 14. The bronchial microbiome was studied by collecting bronchial swabs during necropsy at day 21, when the experiment ended or earlier in case pigs had reached the pre-specified humane endpoint and had to be killed before day 21. Swab samples were prepared and DNA extracted according to an established protocol and then used for metagenomic shotgun sequencing. In this deliverable document, the microbiome analysis results are shown and discussed. The results of the extensive immunological and pathological analyses are revealed in deliverable D7.6.

4. Result 1 bronchial microbiome composition

The top 10 abundant bacterial species included: *Sphingobium YG1*, *Burkholderia contaminans*, *Sphingobium xenophagum*, *Mesomycoplasma flocculare*, *Hydrogenophaga pseudoflava*, *Cutibacterium acnes*, *Acidovorax JMULE5*, *Sphingobium koreensis*, *Acidovorax KKS102* and *Acinetobacter lwoffii*. From these, *B. contaminans*, *S. xenophagum*, *H. pseudoflava*, *A. lwoffii* and *S. koreensis* share a function of all being motile by means of flagella.

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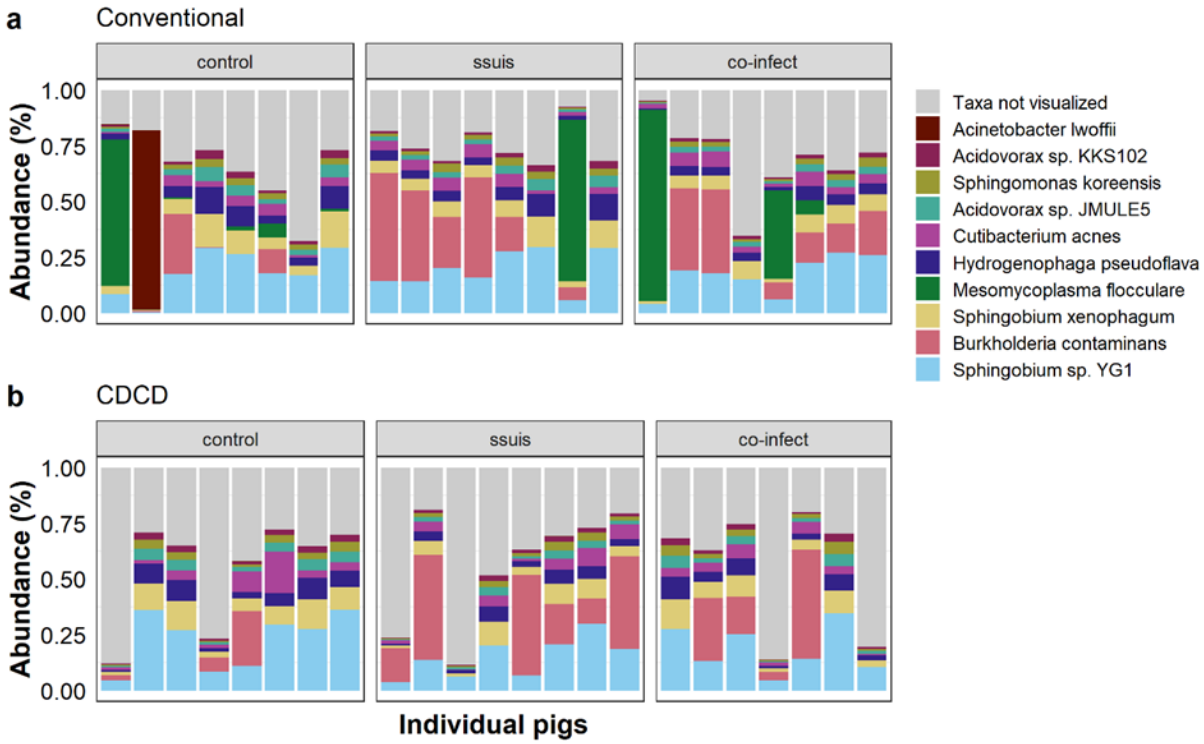

Figure 1 | Association of infection groups and the composition of the bronchial microbiome in conventional or CDCD (caesarean-derived colostrum-deprived) pigs. Relative abundance of the 10 most abundant bacterial species per infection group; control, infected only with *S. suis*, co-infected with both *S. suis* and PRRSV. (**a**) Conventional birth (**b**) CDCD. Bacterial abundance was plotted on the relative abundance scale from 0.00 to 1.00.

5. Result 2. Infection-associated differences in bronchial microbiome

Differential abundance analysis revealed which bacterial species significantly differed in terms of abundance when comparing infection groups to the control group (figure 2). In the conventional born pig groups, ***S. suis*** infection resulted in 5 differentially abundant bacteria in the bronchial microbiome, when compared to the control group. Bacteria with a relative abundance above 0.01% and that changed in terms of relative

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abundance compared to the control group, expressed as log2 fold changes (l2fc), namely the increase of: *Corynebacterium variabile* (2.6 l2fc, 0.12% abundance), *Pediococcus pentosaceus* (2.8 l2fc, 0.06% abundance), *Staphylococcus arlettae* (1.9 l2fc, 0.01% abundance), *Lactococcus raffinolactis* (1.5 l2fc, 0.03% abundance) and *Lactiplantibacillus plantarum* (1.8 l2fc, 0.03% abundance). **Co-infection** resulted in 3 differentially abundant bacteria, namely the increase of: *Glaesserella parasuis* (2.4 l2fc, 0.09% abundance), *Staphylococcus arlettae* (2.2 l2fc, 0.03% abundance) and *Rhodococcus fascians* (1.9 l2fc, 0.03% abundance).

In the CDCD born pig group, ***S. suis*** infection resulted in 15 differentially abundant bacteria in the bronchial microbiome, when compared to the control group. These include a reduction of: *Limosilactobacillus* reuteri (-2.7 l2fc, 0.02% abundance), *Aerococcus urinaeequi* (-2.7 l2fc, 0.05% abundance), *Lactobacillus johnsonii* (-2.0 l2fc, 0.01% abundance), *Providencia* sp. R33 (-3.3 l2fc, <0.005% abundance) and of *Weissella paramesenteroides* (-2.3 l2fc, 0.01% abundance). **Co-infection** resulted in 14 differentially abundant bacteria, including the increase of *Frigoribacterium* sp. NBH87 (1.1 l2fc, % abundance) and a decrease of: *Bacteroides thetaiotaomicron* (-2.5 l2fc, 0.49% abundance), *Limosilactobacillus reuteri* (-3.8 l2fc, 0.04% abundance), *Lactobacillus johnsonii* (-2.9 l2fc, 0.01% abundance), *Providencia* sp. R33 (-2.9 l2fc, <0.005% abundance).

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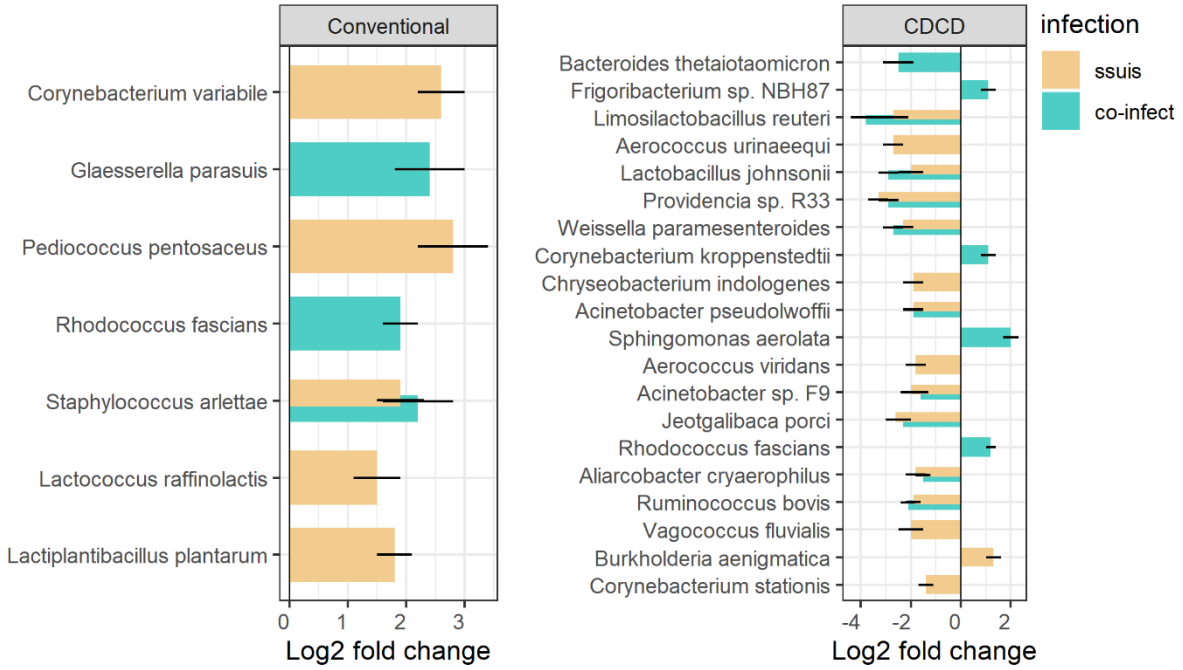

Figure 2| Infection-induced differentially abundant bacteria in the bronchial microbiome for conventional or caesarean-derived colostrum-deprived birth methods. Differential abundance analysis on *S. suis* and *S. suis* & PRRSV co-infection groups as a function of the control group for conventional born (left panel) and CDCD born pigs (right panel). Log2 fold change (l2fc) differences are visualized by bars, coloured according to infection group and the standard error by error bars. Differential abundant bacteria are visualized (p-value < 0.05; abundance > 0.01%; l2fc > |1|) and ordered from most abundant (top) to least abundant (bottom).

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6. Result 3: PRRSV/S. suis infection associated differences in bronchial microbiome

Differential abundance analysis revealed which bacterial species significantly differed in terms of abundance when comparing the *S. suis* infection groups to *S. suis* & PRRSV co-infection group (figure 3). For the conventional birth group, co-infection resulted 6 differentially abundant bacteria in the bronchial microbiome, when compared to the *S. suis* infection group. This included the increase of *Bordetella bronchiseptica* (4.0 l2fc, 4.4% abundance), *Bacteroides heparinolyticus* (1.4 l2fc, <0.005% abundance), *Rhodococcus fascians* (1.6 l2fc, 0.03% abundance) and the decrease of *Prevotella copri* (-2.1 l2fc, 0.08% abundance), *Dorea longicatena* (-2.0 l2fc, 0.01% abundance), *Weissella jogaejeotgali* (-3.7 l2fc, <0.005% abundance). For the CDCD birth group, the abundance of *Corynebacterium stationis* was increased (2.5 l2fc, 0.05% abundance) as a result of co-infection.

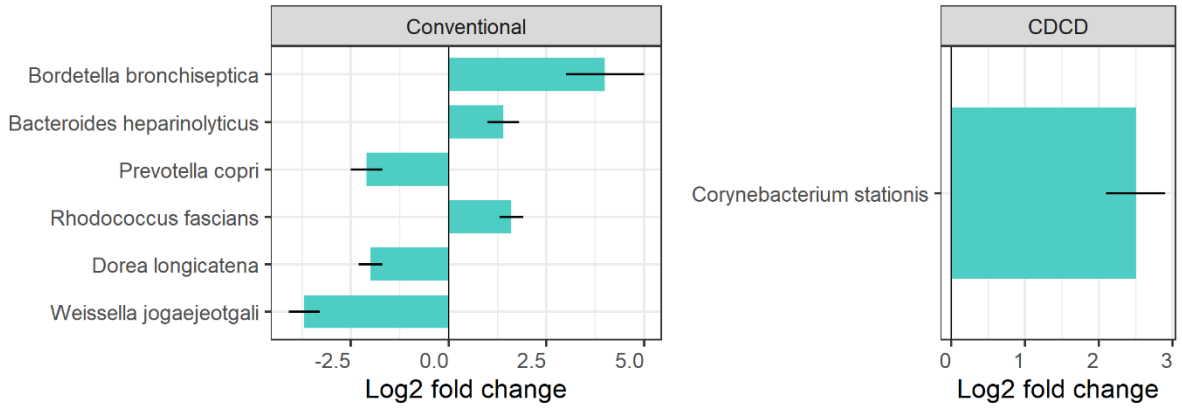

Figure 3| Infection-induced differentially abundant bacteria in the bronchial microbiome for conventional or caesarean-derived colostrum-deprived birth methods. Differential abundance analysis on *S. suis* infection as a function of the *S. suis* & PRRSV co-infection group for conventional birth (left panel) and caesarean-derived colostrum-deprived (right panel). Log2 fold change (l2fc) differences are visualized by bars, coloured according to infection group and the standard error by

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error bars. Differential abundant bacteria are visualized (p-value < 0.05; abundance > 0.01%; l2fc > |1|) and ordered from most abundant (top) to least abundant (bottom).

Summarized, these findings mostly involve bacteria that are present in low abundance (below 0.5% abundance), except for *B. bronchiseptica*, which is present in high abundance in the conventional birth co-infection group, compared to the *S. suis* infection group (figure 4).

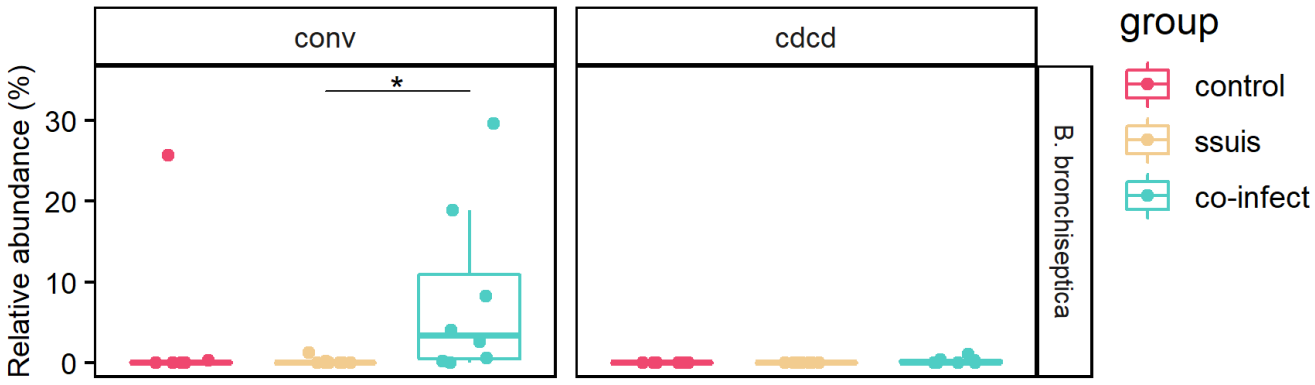

Figure 4 | Co-infection-induced differentially abundant *Bordetella bronchiseptica*. Relative abundance of *Bordetella bronchiseptica* per infection group. Individual pigs are coloured according to infection group; (1) control; (2) infected with *Streptococcus suis*, (3) co-infected with both *S. suis* as PRRSV. Adjusted p-values are calculated as part of ANCOMBC as function of the *S. suis* group and indicated by *< 0.05.

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7. Conclusions

In this study, we determined the bacterial microbiome of pigs born either via conventional birth and raised during farrowing with their mother sow or as caesarean-derived colostrum-deprived pigs raised in an initial sterile environment by using metagenomic shotgun sequencing. We evaluated to what extend a viral infection by PRRSV followed by a *Streptococcus suis* and a *S. suis* infection alone modulates the bronchial microbiome composition, compared to a control group. The results confirmed that the viral/bacterial co-infection and the bacterial infection alone can induce significant differences in the relative abundance of a total of 27 bacterial species compared to the control group. Furthermore, a *S. suis* infection induced a different microbiome composition when preceded by a PRRSV infection, compared to the *S. suis* infection alone. As expected, the microbiological background after birth – farm versus biosafety (level 2) containment – determined the composition of the bronchial lung microbiome in control pigs of each of the two groups and resulted in differences in the microbiome composition after PRRSV/*S. suis* consecutive co-infection and *S. suis* infection alone.

The conventional birth pigs showed an increase of *Staphylococcus arlettae* as a result of *S. suis* infection and co-infection, compared to the control group. *S. arelettae* is considered a commensal bacterial species, but depending on gene composition can also behave as a pathogen (5). Further insights into its genomic composition is required in order to conclude its pathogenicity. PRRSV/*S. suis* co-infection also resulted in an increased abundance of *Glaesserella parasuis*, an important pig pathogen, and of *Rhodococcus fascians* a plant-associated bacterium. *S. suis* infection alone furthermore resulted in an increased abundance of the three lactic acid bacteria *Pediococcus pentosaceus*, *Lactococcus raffinolactis*, *Lactiplantibacillus plantarum* and

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of *Corynebacterium variabile*, a lactate metaboliser (6). Compared to the *S. suis* infection group, co-infection furthermore resulted in an increase of *Bordetella bronchiseptica*, an opportunistic pathogen in pigs (7). Co-infection additionally resulted in an increase of *Bacteroides heparinolyticus*, with a yet unknown function, and of *R. fascians*. Co-infection furthermore resulted in the decrease of three species that are considered commensals: *Prevotella copri*, *Dorea longicatena* and *Weissella jogaejeotgali* (8-10).

In the CDCD group, a large number of microbes changed in term of abundance as a result of infection, compared to the control group. *S. suis* infection only and viral/bacterial co-infection, both decreased the abundance of lactic acid *bacteria Limosilactobacillus reuteri*, *Lactobacillus johnsonii* and of *Providencia* sp. R33, which may produce lactic acid as well. Co-infection also resulted in a decrease of *Bacteroides thetaiotaomicron*, a human symbiont and increase of *Frigoribacterium* sp. NBH87, a soil-associated bacterium (11). *S. suis* infection alone furthermore resulted in a decrease of *Weissella paramesenteroides*, a commensal bacteria, and of *Aerococcus urinaeequi*, which is an opportunistic pathogen in humans (12). Compared to the *S. suis* infection group, viral/bacterial co-infection led to an increase of *Corynebacterium stationis*, which is considered a potential pathogen in humans (13).

The analysis of the bronchial microbiome concluded that a small group of bacteria is present in high abundance (figure 1). Differentially abundant bacteria that were detected as a result of co-infection involved the increase of *B. bronchiseptica* in the conventional birth group. Genomic analysis is currently being performed in order to confirm this species. In addition, a large number of other bacteria were found to be differentially abundant, but these are present in low abundance (below 0.5% abundance). It is therefore unknown if these other bacteria are also biologically

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relevant. In case that these lowly abundant bacteria can affect pig health, the observed differences in *Glaesserella parasuis* and *Staphylococcus arlettae* should be further investigated.

The further analyses of pathological and immunological changes in this study (see D7.6) will reveal a possible association between the observed changes in microbiome composition before and after infection and the immune response and the disease course after infection.

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8. Annexes

Table 1| Infection-induced differentially abundant bacteria in the bronchial microbiome for conventional or cesarean-derived colostrum-deprived birth methods compared to the control group.

Conventional

Species	infection	l2fc	se	padj
Corynebacterium variabile	ssuis	2.6	0.4	0.0000
Glaesserella parasuis	co-infect	2.4	0.6	0.0089
Staphylococcus arlettae	co-infect	2.2	0.6	0.0378
Pediococcus pentosaceus	ssuis	2.8	0.6	0.0011
Rhodococcus fascians	co-infect	1.9	0.3	0.0000
Lactococcus raffinolactis	ssuis	1.5	0.4	0.0047
Lactiplantibacillus plantarum	ssuis	1.8	0.3	0.0000
Staphylococcus arlettae	ssuis	1.9	0.4	0.0005

CDCD

Species	infection	l2fc	se	padj
Bacteroides thetaiotaomicron	co-infect	-2.5	0.6	0.0463
Frigoribacterium sp. NBH87	co-infect	1.1	0.3	0.0000
Limosilactobacillus reuteri	co-infect	-3.8	0.6	0.0000
Limosilactobacillus reuteri	ssuis	-2.7	0.6	0.0008
Aerococcus urinaeequi	ssuis	-2.7	0.4	0.0000
Lactobacillus johnsonii	co-infect	-2.9	0.4	0.0000
Lactobacillus johnsonii	ssuis	-2	0.5	0.0417
Providencia sp. R33	co-infect	-2.9	0.4	0.0000
Providencia sp. R33	ssuis	-3.3	0.4	0.0000
Weissella paramesenteroides	co-infect	-2.7	0.4	0.0000
Weissella paramesenteroides	ssuis	-2.3	0.4	0.0001
Corynebacterium kroppenstedtii	co-infect	1.1	0.3	0.0447
Acinetobacter pseudolwoffii	co-infect	-1.9	0.4	0.0002
Chryseobacterium indologenes	ssuis	-1.9	0.4	0.0010
Acinetobacter pseudolwoffii	ssuis	-1.9	0.4	0.0081
Sphingomonas aerolata	co-infect	2	0.3	0.0000
Acinetobacter sp. F9	co-infect	-1.6	0.3	0.0000
Jeotgalibaca porci	co-infect	-2.3	0.3	0.0000
Aerococcus viridans	ssuis	-1.8	0.4	0.0008
Jeotgalibaca porci	ssuis	-2.6	0.4	0.0000
Acinetobacter sp. F9	ssuis	-2	0.4	0.0000
Rhodococcus fascians	co-infect	1.2	0.2	0.0001
Ruminococcus bovis	co-infect	-2.1	0.3	0.0000
Aliarcobacter cryaerophilus	co-infect	-1.5	0.3	0.0000

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Vagococcus fluvialis	ssuis	-2	0.5	0.0200
Aliarcobacter cryaerophilus	ssuis	-1.8	0.4	0.0000
Ruminococcus bovis	ssuis	-1.9	0.3	0.0000
Burkholderia aenigmatica	ssuis	1.3	0.3	0.0005
Corynebacterium stationis	ssuis	-1.4	0.3	0.0171

Table 2| Viral/bacterial co-infection-induced differentially abundant bacteria in the bronchial microbiome for conventional or cesarean-derived colostrum-deprived birth methods compared to the *Streptococcus suis* infection group.

Conventional

Species	infection	l2fc	se	padj
Bordetella bronchiseptica	co-infect	4	1	0.0443
Bacteroides heparinolyticus	co-infect	1.4	0.4	0.0000
Prevotella copri	co-infect	-2.1	0.4	0.0000
Rhodococcus fascians	co-infect	1.6	0.3	0.0001
Dorea longicatena	co-infect	-2	0.3	0.0000
Weissella jogaejeotgali	co-infect	-3.7	0.4	0.0000

CDCD

Species	infection	l2fc	se	padj
Corynebacterium stationis	co-infect	2.5	0.4	0.0000

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