

Friends, enemies and everything in between

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VALORIZATION

RELEVANCE AND SOCIETAL IMPACT

This thesis provides knowledge generation around cutting-edge microbiome research - the vaginal microbiota (VMB) - and information on prevalence status of some the most fastidious and long-lasting sexually transmitted infections (STIs) in sub-Saharan African women. Via a systematic search our work confirms that for most of the pregnant women living in sub-Saharan Africa, the VMB composition is *Lactobacillus* dominant (**chapter 2**). This is also the case among the pregnant women in Pemba Island, Tanzania, this thesis's chosen research setting (**chapter 7**). In this very same population, *Chlamydia (C.) trachomatis*, *Neisseria (N.) gonorrhoeae*, *Trichomonas (T.) vaginalis*, *Mycoplasma (M.) genitalium*, and human papillomaviruses (HPV) was present during and after parturition (**chapter 4-7**). Moreover, a high frequency of VMB dysbiosis (defined as non-*Lactobacillus* dominant VMB) was observed post-delivery in this population (**chapter 7**). These findings expand scientific knowledge, for clinicians, researchers, and public health officials, on vastly under-research topics: vaginal conditions (vaginal dysbiosis, bacterial vaginosis, and aerobic vaginitis) and STIs in low- and middle-income countries, especially those belonging to the STI endemic areas in sub-Saharan Africa. It also highlights their burden in a vulnerable population, namely pregnant women. Therefore, it is essential to further research and monitor STIs' burden and VMB composition in pregnant women, their role on health outcomes and implement up-to-date strategies to better control and eliminate STIs ad vaginal dysbiosis, particularly so during pregnancy.

Regrettably, despite continued public health efforts, maternal and neonatal morbidity and mortality remain high in sub-Sahara Africa. There is also increasing evidence related to the contribution of STIs, VMB dysbiosis, or VMB dysbiotic conditions, such as bacterial vaginosis (BV) on maternal and neonatal morbidity (**chapter 3**). This evidence is yet to be confirmed in the Pemban population. Nevertheless, the novel scientific knowledge about the VMB composition in expectant and new mothers from Pemba should be used as a stepping stone for upcoming pregnancy and VMB-related research in sub-Saharan African communities (**chapter 7**). Additional research on this topic will ultimately provide evidence whether and how VMB composition is of clinical utility and can assist in making evidence-based VMB-related strategies to improve maternal and neonatal health.

This work is part of a collaborative effort between the Institute of Public Health Genomics (Maastricht, the Netherlands), the Public health laboratory - Ivo de Carneri (Pemba Island, Tanzania) and the Center for Public Health Kinetics (India). This thesis provides the earliest testing results output of this collaboration (**Chapter 4, 5,6 and 7**). In order to maximize and continue this effort, different approaches will be sustained or further reinforced;

1. More plans for knowledge and skills transfer and for capacity strengthening between the local setting in Pemba and other international stakeholders involved are planned in the near future, or as soon as the international travels are allowed.
2. Fostering international connections between the Pemba Biobank and European institute, such as Maastricht University, Maastricht University Medical Center (MUMC+), and the University Medical Center Amsterdam will be strengthened.

Furthermore, additional samples (from a total of up to 600 women) in the Biobank in Pemba are available and will be part of the next shared research efforts. The availability of these samples and related clinical information will offer opportunities to expand the research in Pemba, will continue collaborations with partners such as our research group, shared efforts in requests for funding, with the ultimate goal to identify clinically relevant associations with the potential to impact the local population.

There are also multiple options for follow-up research based on these primary results. This research can for instance be a starting point for further research in the field of infectious diseases and host-pathogens interactions, with the option to:

- Investigate bacterial serovars of *Chlamydia trachomatis*; including the one responsible for trachoma
- Detect and characterize other genital pathogens (*Waddlia chondrophila*, *Lymphogranuloma venereum* (LGV) *Ureaplasma* species, *Mycoplasma hominis*, *Treponema pallidum*, *Candida* species, Herpes simplex virus 1 (HSV1) and Herpes simplex virus 2 (HSV2))
- Investigate possible Antimicrobial Resistance (AMR) carried by the detected pathogens
- Further investigate the antibiotic usage in Pemba
- Assess the host-genetic determinants of infections
- Investigate the relationship between VMB and genital pathogens with adverse pregnancy outcomes

These and subsequent research outcomes from biobanking activities have the potential to inform future policymaking in the field of public health and mother and child health care. Among the ultimate goals are efforts to lower the prevalence of STI on the Island (e.g. by using more efficient screening strategies), reduce the morbidity caused by these pathogens, and lower the amount of vertical transmission of STIs or other vaginal pathogens from mother to newborn.

SCIENTIFIC INNOVATION AND IMPLEMENTATION

As observed in **chapter 2** and **3**, VMB data in pregnancy among women from sub-Saharan Africa is scant, highlighting the need for further research on the topic. Since VMB composition differ within and between women (due to several factors, as discussed in **chapter 8**), a larger dataset

will provide more definite insights on VMB composition in a population and its role in health. As expansion of this clinical samples set will be a first contribution in this direction.

The findings and key discussions in this thesis might serve as a starting ground on which bases new strategies and approaches can be developed and might be of interest for various stakeholders involved in the advancements or manufacturing of (commercial) VMB or STI testing kits. In the work described in this thesis, previously validated samples collection and testing kits for genital infections (i.e. swabs and eNAT buffer, IS-pro assay for VMB, Presto *C. trachomatis*, *N. gonorrhoea*, and *T. vaginalis* kit, and Atila AmpFire HPV isothermal PCR kit) were used providing evidence that they can be used also on samples collected in this biobank setting. The new Atila AmpFire for the HPV detection might be in particular a very compelling detection method for many low-resource laboratory settings as the kit includes the materials and protocol for a quick DNA isolation process. Unfortunately, in this project we did not use the DNA isolation protocol as the DNA were already isolated for the non-viral STI testing. Thus, investigating the utility and practicality of the Atila Ampfire HPV kit and other similar STI testing kits in a low-resource laboratory setting is still warranted. Nevertheless, such methodological innovations will hopefully pave the way towards easier and more affordable molecular diagnostics tools that might be also be widely-implemented for future use in low- and middle-income countries. Easier diagnostic tools such as rapid nucleic acid amplification tests (NAATs) and point of care (POC) testing can improve healthcare, in this case particularly for expectant mothers.

Research around VMB diversity, particularly in expectant mothers, is still at an early stage and its link to health outcomes needs to be further clarified. Nevertheless, in the last decade new evidence has been increasingly shared on the association between VMB and reproductive health. Several studies have suggested that urogenital microbiome composition might predict reproductive technology success and early pregnancy health (**chapter 3**). The link between VMB and later pregnancy complication, such as preterm birth, appears less clear and more research is needed. However low- and middle-income countries, especially those with high burden of adverse pregnancy outcomes, would greatly benefit from research that are investigating causes and factors contributing to this burden. If relevant association with pregnancy-related health burdens are found, they can hopefully contribute means to tackle those burdens.

At this early VMB research stage, various stakeholders in the public and private sector should continue to develop state of the art methods for VMB analysis. Alike, innovative STI testing will offer new research opportunities. It will remain of utmost important that public health official constantly evaluate healthcare options to improve maternal and newborn health, especially the latest evidence based STI and VMB methods and strategies from both the private and the public scientific community.