Secrets of early life revealed from less than half a teaspoon of blood

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A global team of scientists have mapped the developmental pathway of a newborn's life for the first time. The research, published in *Nature Communications*, could transform our understanding of health and

disease in babies.

Co-led by the MRC Unit The Gambia at the London School of Hygiene & Tropical Medicine, the new study included lifting the lid on what genes are turned on, what proteins are being made and what metabolites are changing in the first seven days of human life.

Newborn babies are the most vulnerable population when it comes to infectious disease. Establishing key pathways in early development could help measure the impact of factors such as diet, disease and maternal health, as well as key interventions like vaccines.

The study was conducted by the Expanded Program on Immunization Consortium (EPIC) research team, which includes MRC Unit The Gambia at the London School of Hygiene & Tropical Medicine, Boston Children's Hospital, the University of British Columbia, and the Papua New Guinea Institute of Medical Research.

The first week of a newborn's life is a time of rapid biological change as the baby adapts to living outside the womb, suddenly exposed to new bacteria and viruses, yet surprisingly little is known about these early changes. One of the biggest challenges in gathering data on newborn development has been sourcing a large enough blood sample for comprehensive profiling from a tiny newborn. The team overcame this with pioneering laboratory techniques applied on less than half a teaspoon of blood.

By using sophisticated software and new approaches they integrated different kinds of measurements to interpret the complex data derived from the precious samples. Thousands of changes over the first week of life were found including in gene expression and components involved in immunity.

Senior author Beate Kampmann, Professor of Paediatric Infection and Immunity from the London School of Hygiene & Tropical Medicine and Director of its Vaccine Centre, said: "Up to two thirds of newborn deaths can be prevented if effective health measures are provided at birth and during the first week of life. Of the 5.4 million under-five child deaths per year, about half occur during the neonatal period, i.e. the first month of life.

"Knowledge about key developmental processes during our earliest days remains sparse, but this study plugs some of those crucial gaps. This work is particularly important for vaccine research. Newborns have very limited protection from infection in early life and there is an urgent need to optimise protective measures, including vaccines, used in this age group."

Working closely with local communities, the research team recruited newborns in a health centre in The Gambia, West Africa. They took blood samples from the babies on the day of birth, and then again either on day one, three or seven.

The samples were processed in the collaborating laboratories in Africa and North America, where the researchers discovered dramatic molecular changes driven by development. The findings were then validated in a second group of Australasian newborns. The two independent cohorts were found to have common, highly dynamic developmental trajectories, suggesting that the changes do not occur at random, but instead follow an age-specific pathway.

Prof Kampmann said: "The MRC Unit in The Gambia has carried out important studies in newborns for a long time in order to optimize the use of vaccines. Given our excellent community relations and infrastructure, we were ready to partner with our collaborators to apply the new tools of systems biology to very small blood samples. We

wanted to establish this work in a real world situation in order to gain insight into immune development in a setting where new interventions can have the biggest impact on newborn survival."

Ofer Levy, Director of the Precision Vaccines Program at Boston Children's Hospital and a senior author on the paper, said: "Most infections in the world occur early in life, and newborns have the greatest susceptibility and the worst outcomes. This work provides a valuable window into health and disease in the first week of life. Our exciting findings allows us to ask bigger questions about the differences between different populations and the impact of biomedical interventions such as vaccines on development.

"Currently, most vaccines are developed by trial and error. We seek deep molecular insight into vaccine function in early life so we can better develop infant vaccines for the future. We demonstrated that it's possible to recruit newborns in a resource-poor setting, obtain small amounts of their blood, process it, ship it, conduct systems biology assays and integrate the results—turning big data into knowledge."

Going forward, the EPIC team is currently investigating the impact of different vaccines on this early developmental trajectory in a larger cohort in The Gambia and Papua New Guinea.

The authors acknowledge limitations of their study including validation in larger cohorts and increasing our functional insights into the discovered pathways.

More information: Dynamic molecular changes during the first week of human life follow a robust developmental trajectory, *Nature Communications* (2019). DOI: 10.1038/s41467-019-08794-x , www.nature.com/articles/s41467-019-08794-x

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