Swiss TPH
Swiss Tropical and Public Health Institute
Schweizerisches Tropen- und Public Health-Institut
Institut Tropical et de Santé Publique Suisse

Clinical Immunology Unit

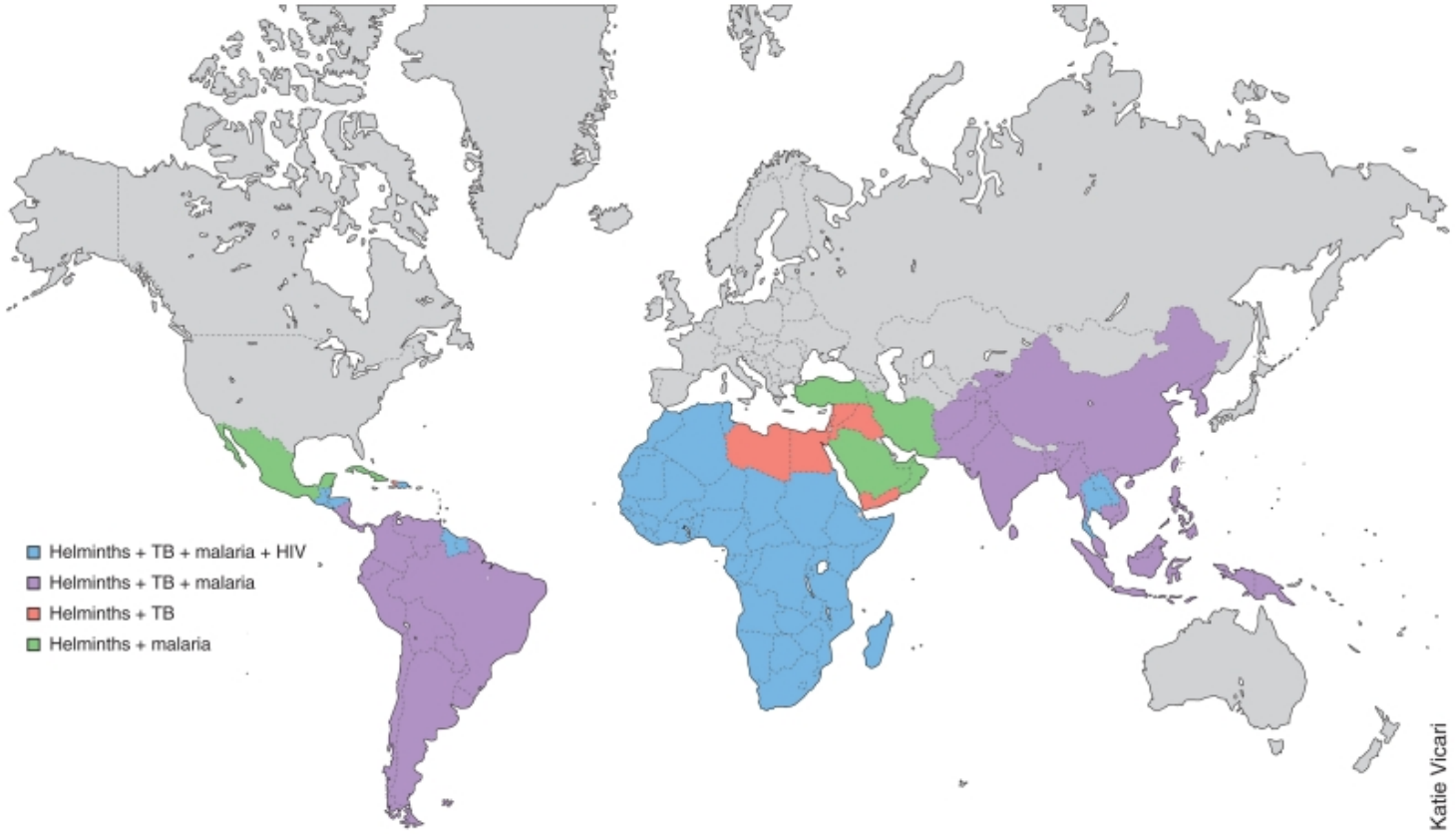
Tuberculosis and Helminth Co-Infections in Tanzanian Adults

Claudia A. Daubenberger

Swiss TPH Symposium 2017

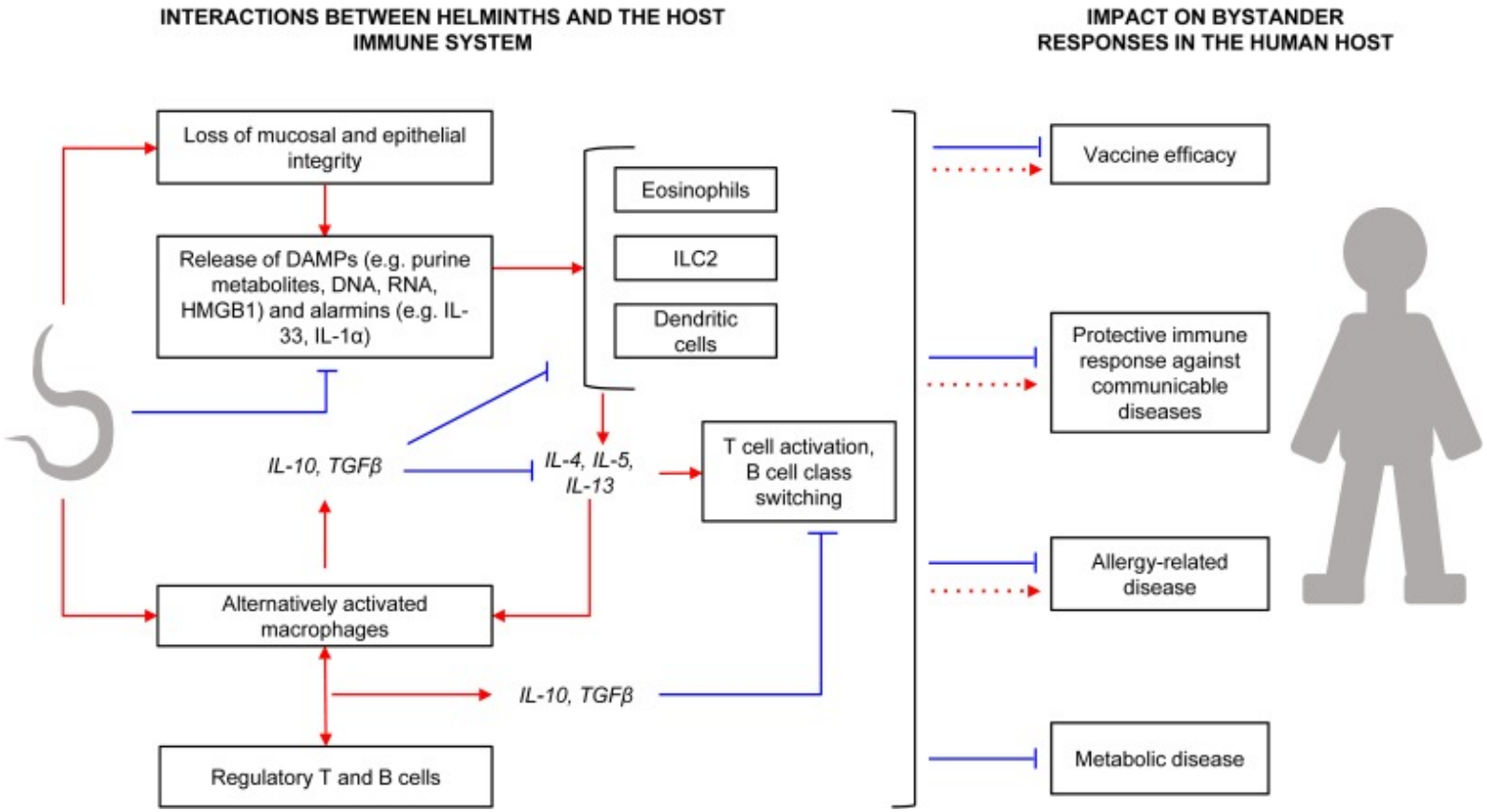
8.12.2017

World map showing the geographic distribution of coinfection with helminths together with tuberculosis, malaria and/or HIV infection of adults



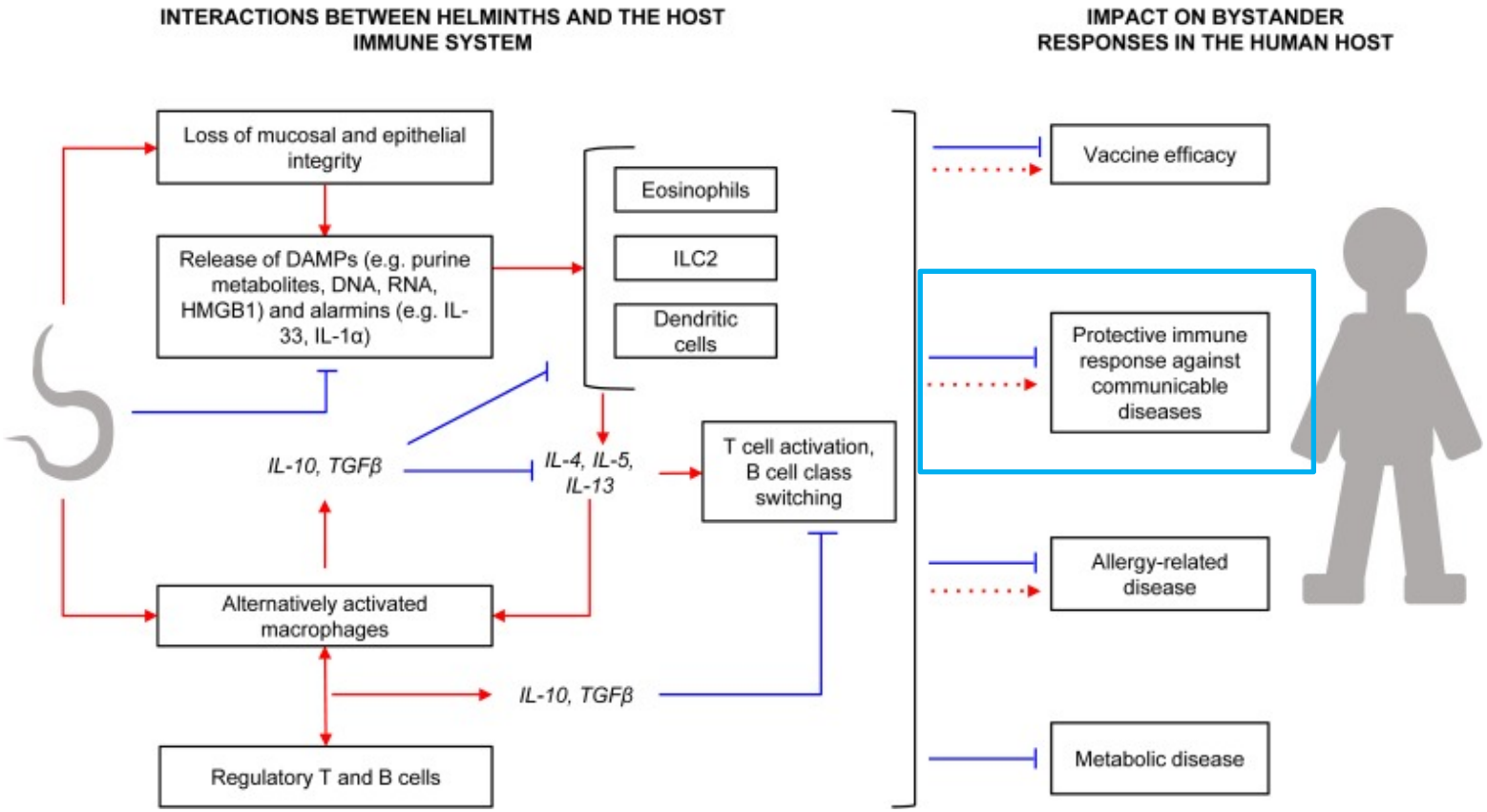
Taken from PMID: 24145791

Interaction between helminths and host immune system: bystander responses are affected by the helminth infection



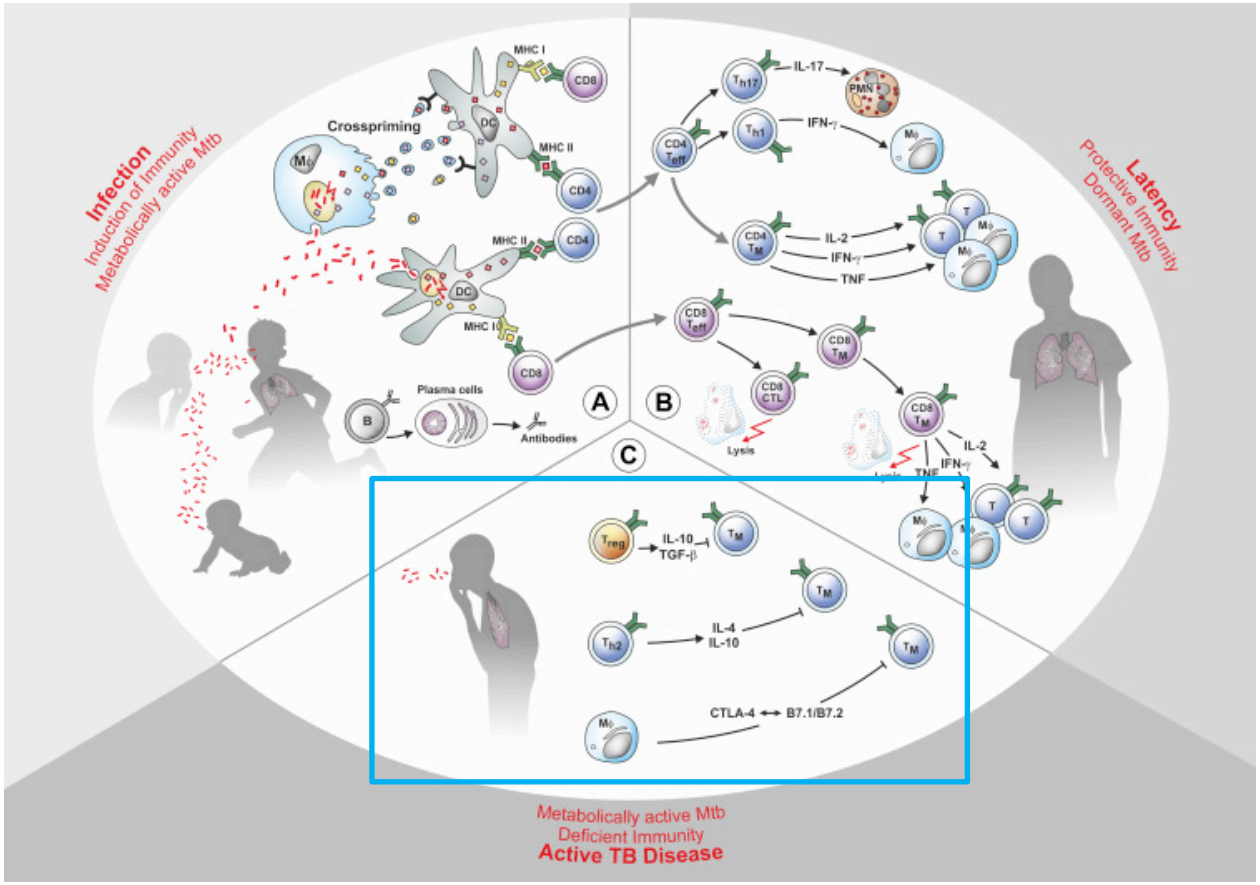
Red arrows: positive effects,
Blue lines: supressive effects

Interaction between helminths and host immune system: bystander responses are affected by the helminth infection



Red arrows: positive effects,
Blue lines: supressive effects

Phases of human immune responses against *Mycobacterium tuberculosis* infections in lungs of affected people



Kaufmann et al., 2016

Aims of study:

i) to delineate *Mtb*-specific T-cell responses in patients with pulmonary tuberculosis (TB) and helminth co-infection from two Sub-Saharan countries, *e.g*. Tanzania (TZ) and South Africa (SA)

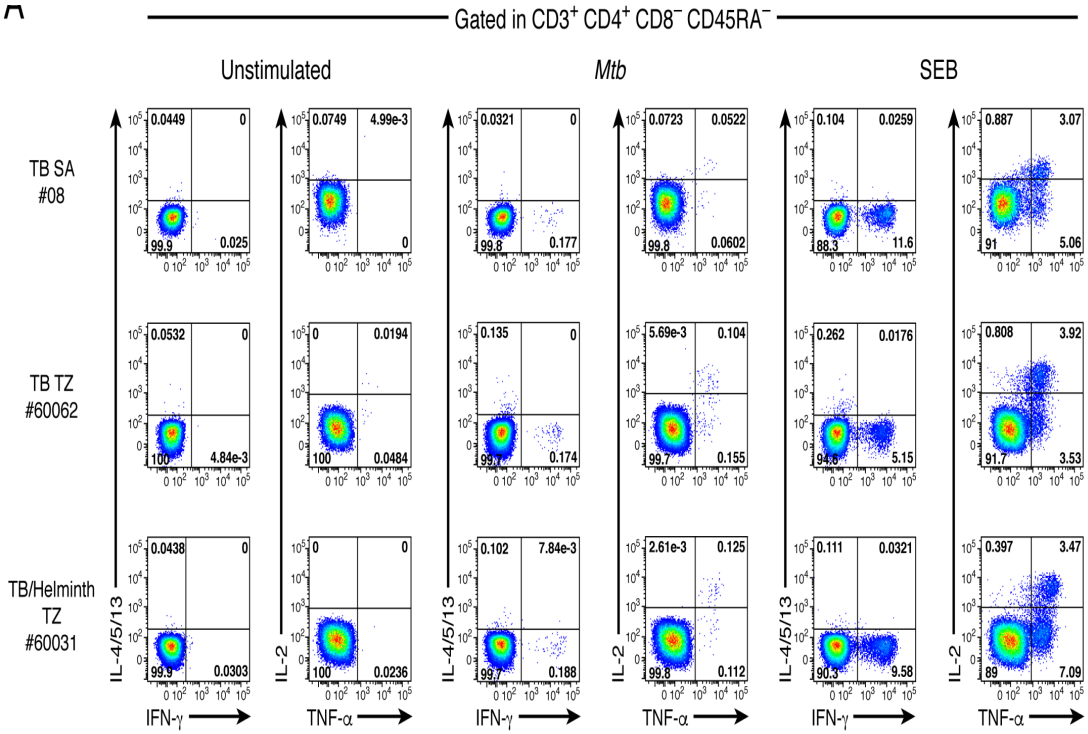
ii) to determine the influence of ongoing or past helminth infections on *Mtb*-specific T-cells responses.

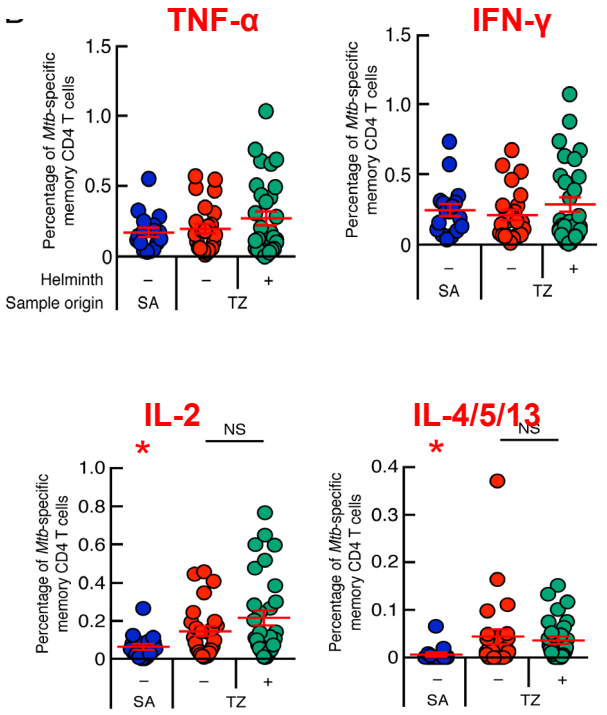
ID	Origin	Number	Mean Age	Gender	Helminth infection	BCG vaccination status
Clinical TB SA	South Africa	17	36	3F/12M	11% past exposure	17/17 (100%)
Clinical TB TZ	Tanzania	25	29	9F/16M	28% past exposure	25/25 (100%)
Clinical TB/ helminth TZ	Tanzania	30	30	6F/24M	Ongoing	30/30 (100%)

Table: Demographic and clinical data of cohort analysed.

Amelio et al., 2017

Mtb-specific CD4 T cells from TB patients from TZ have mixed Th1/Th2 cytokine profile

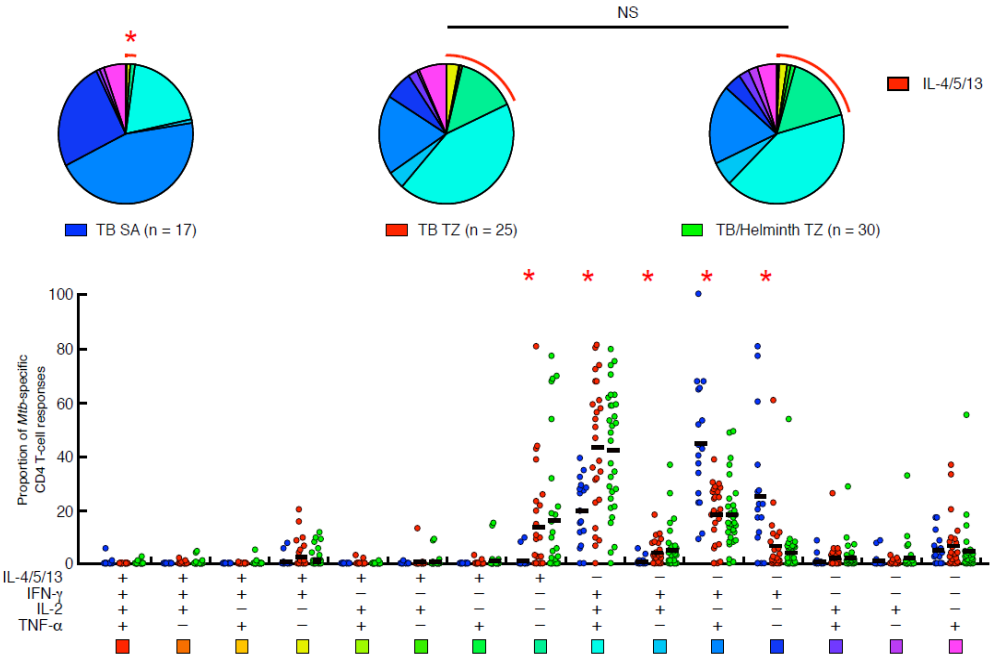


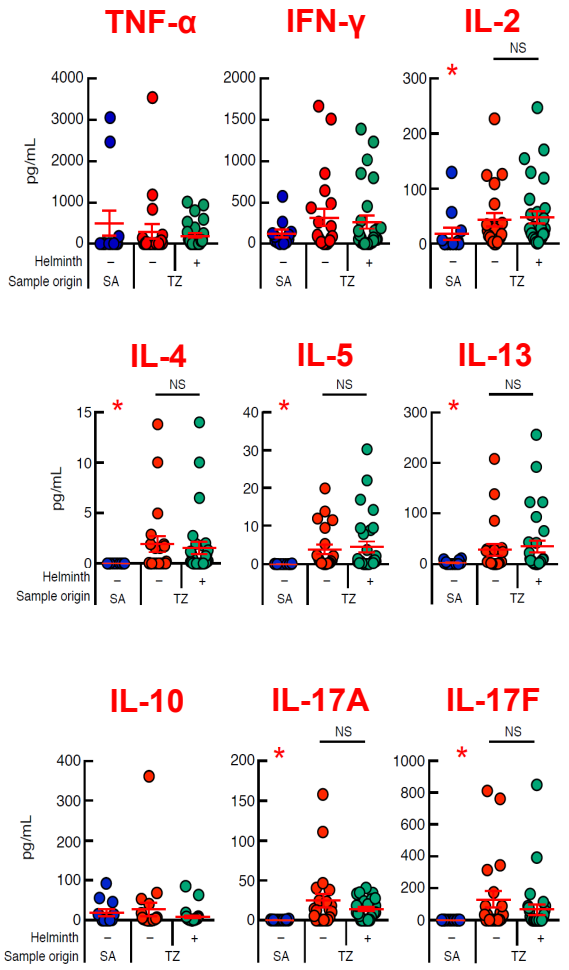


Blue: TB patients from SA
Red: TB patients from TZ
Green: *Mtb*/helminth co-infected patients
Red stars indicate statistical significance. Statistical significance (* = $P<0.05$)

Amelio et al., 2017

Mtb-specific CD4 T cells from TB patients from TZ have mixed Th1/Th2 cytokine profile



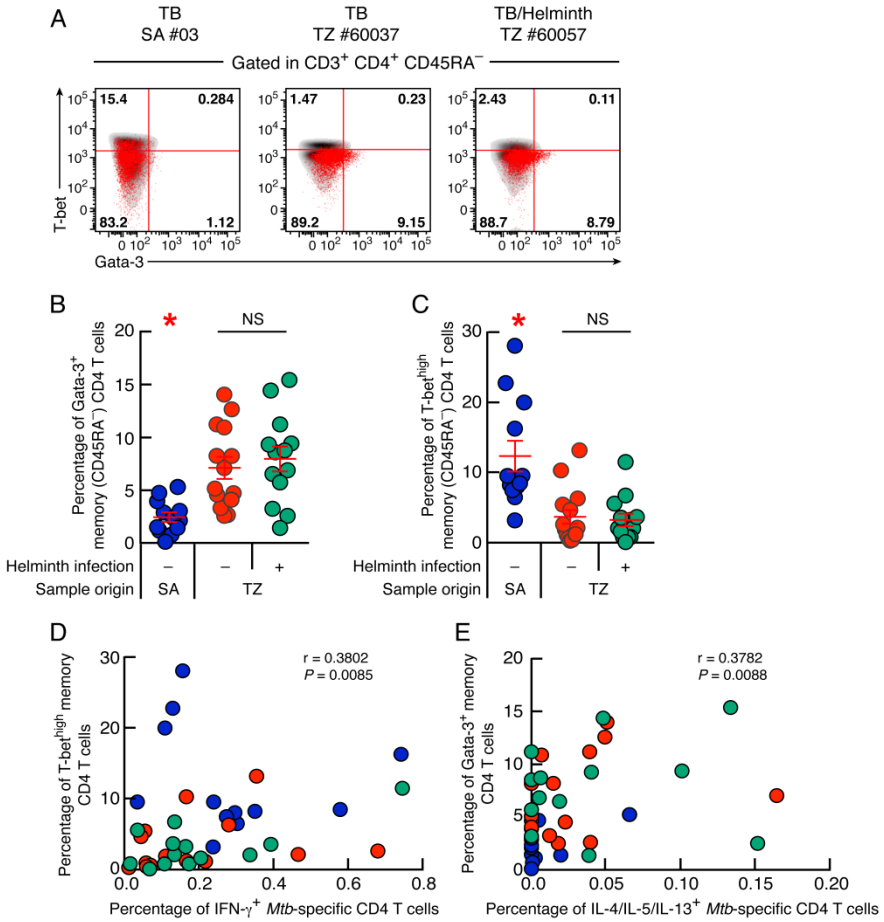


Blue: TB patients from SA
Red: TB patients from TZ
Green: *Mtb*/helminth co-infected patients
Red stars indicate statistical significance.
Statistical significance (* = $P<0.05$)

Amelio et al., 2017

Swiss TPH

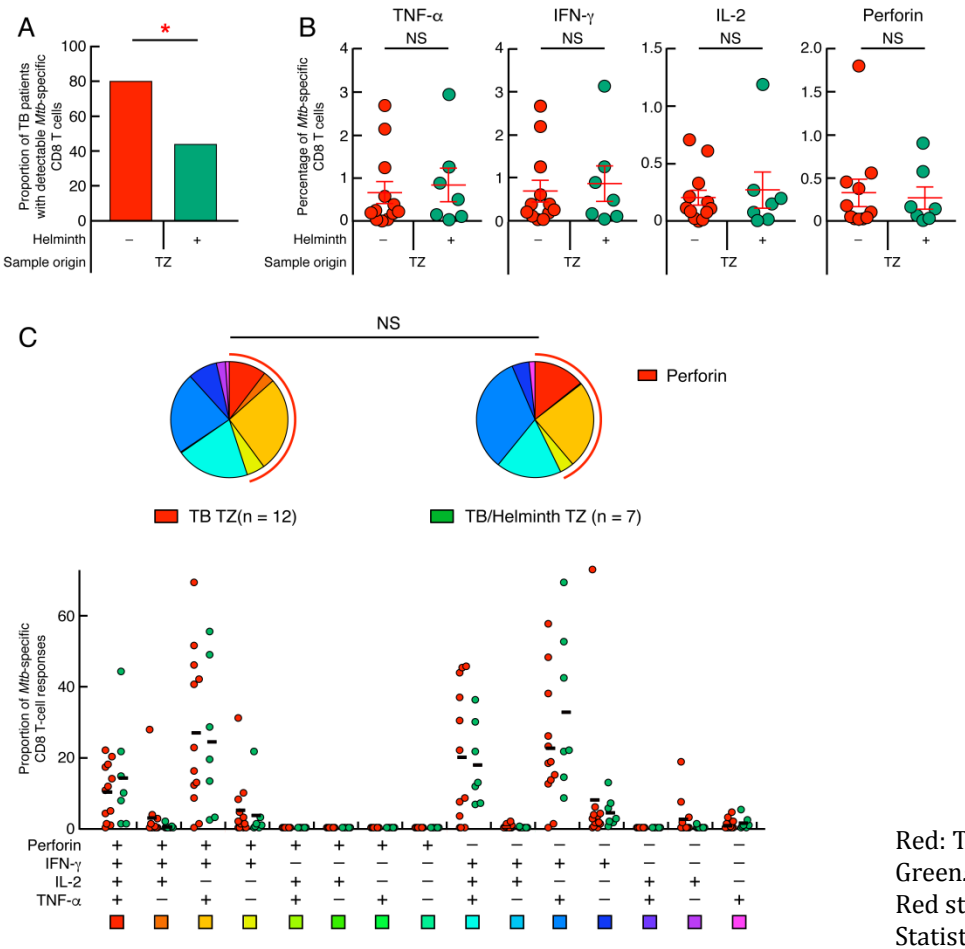
Memory *Mtb*-specific CD4 T cells of TB patients from TZ harbor increased Gata-3 (Th2 CD4 cell lineage marker) and reduced T-bet (Th1 CD4 cell lineage marker) expression



Blue: TB patients from SA
Red: TB patients from TZ
Green: *Mtb*/helminth co-infected patients
Red stars indicate statistical significance.
Statistical significance (* = $P<0.05$)

Amelio et al., 2017

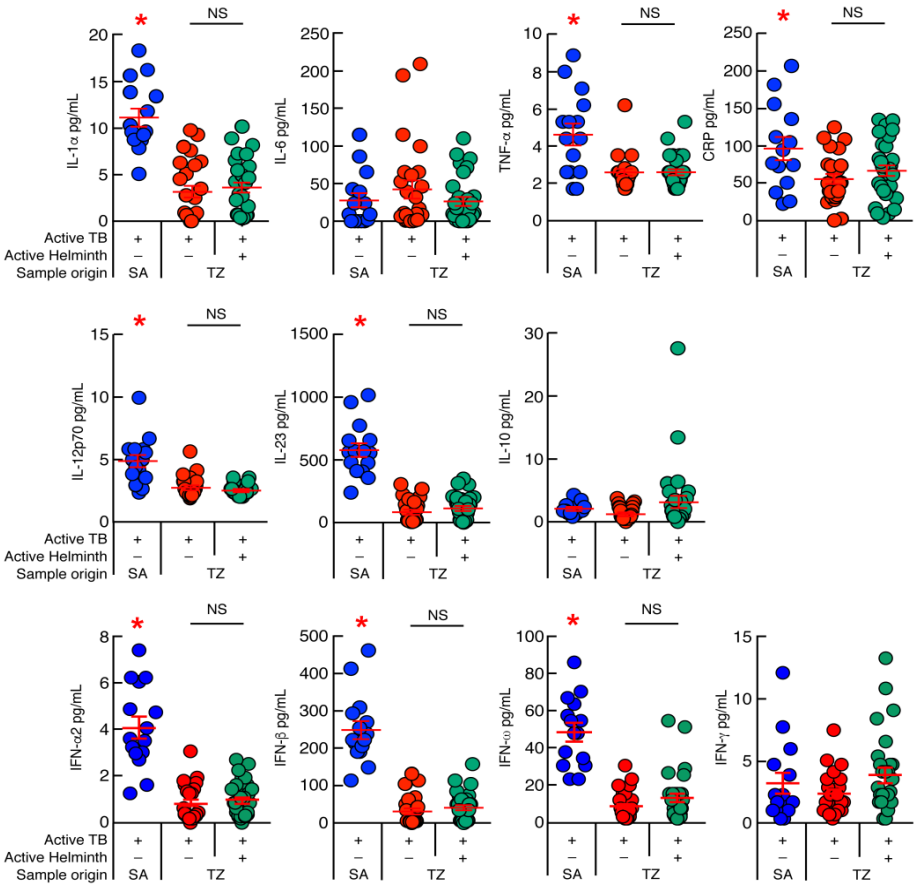
Reduced proportion of patients with detectable *Mtb*-specific CD8 T cells in clinical TB cases from TZ with ongoing helminth co-infected patients:



Amelio et al., 2017

Red: TB patients from TZ
Green*: Mtb*/helminth co-infected patients
Red stars indicate statistical significance.
Statistical significance (* = $P<0.05$)

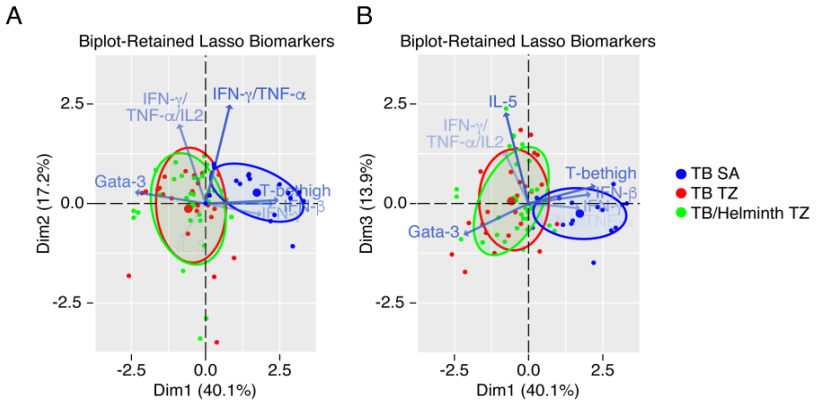
Systemic inflammation markers in serum of clinical TB patients from TZ and SA with or without ongoing helminth infections

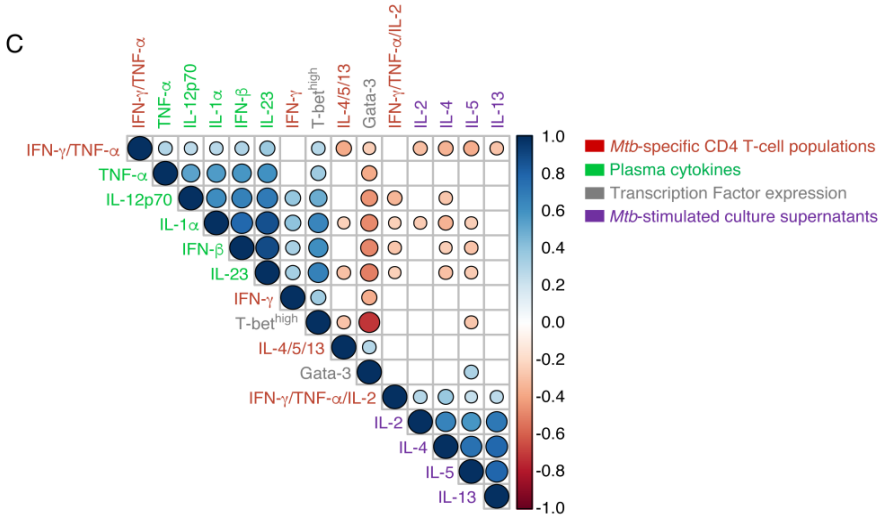


Blue: TB patients from SA
Red: TB patients from TZ
Green: *Mtb*/helminth co-infected patients
Red stars indicate statistical significance.
Statistical significance (* = $P<0.05$)

Amelio et al., 2017

Th1 cytokine profiles in *Mtb*-specific CD4 T cells are positively associated with elevated systemic inflammation markers





Amelio et al., 2017

Axes	Variance (%)	Immune parameters	Correlation	*P* value
Dim1	36.6%	T-bet^{high}	0.827	3.4E-19
Dim1	36.6%	IFN-β	0.767	3.9E-15
Dim1	36.6%	IFN-γ	0.635	2.1E-09
Dim1	36.6%	IFN-γ/TNF-α	0.277	0.018
Dim1	36.6%	IL-5	-0.284	0.018
Dim1	36.6%	IFN-γ/TNF-α/IL2	-0.303	0.010
Dim1	36.6%	Gata-3	-0.800	3.5E-17
Dim2	18%	IFN-γ/TNF-α	0.835	7.5E-20
Dim2	18%	IFN-γ/TNF-α/IL2	0.670	1.2E-10
Dim2	18%	IL-5	-0.302	0.010
Dim3	15%	IL-5	0.838	4.2E-20
Dim3	15%	IFN-γ/TNF-α/IL2	0.483	1.7E-05
Dim3	15%	Gata-3	-0.288	0.014

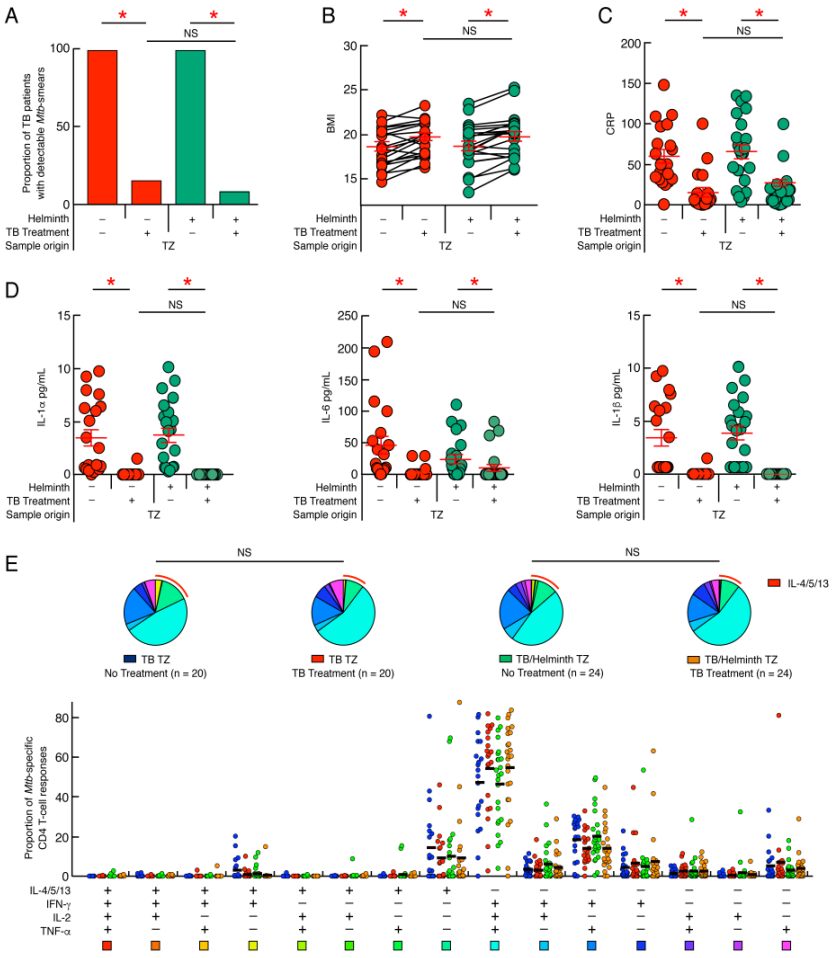
Abbreviations: T-bet^{high}, percentage of memory CD4 T cells expressing high level of T-bet; IFN-β, serum level of IFN-β; IFN-γ, proportion of single IFN-γ producing *Mtb*-specific CD4 T cells; IFN-γ/TNF-α, proportion of dual IFN-γ/TNF-α producing *Mtb*-specific CD4 T cells; IL-5, level of IL-5 detected in supernatants of *Mtb*-stimulated cell cultures; IFN-γ/TNF-α/IL-2, proportion of polyfunctional IFN-γ/TNF-α/IL-2 producing *Mtb*-specific CD4 T cells; Gata-3, percentage of memory CD4 T cells expressing Gata-3.

https://doi.org/10.1371/journal.pntd.0005817.t002

Serum cytokine profiles and the *Mtb*-specific immune signatures of TB patients from SA and TZ are significantly different

Blue: TB patients from SA
Red: TB patients from TZ
Green: *Mtb*/helminth co-infected patients
Red stars indicate statistical significance.
Statistical significance (* = P<0.05)

Influence of ongoing helminth infection on TB treatment efficiency assessed 60 days past TB treatment initiation



Red: TB patients from TZ
Green: *Mtb*/helminth co-infected patients
Red stars indicate statistical significance.
Statistical significance (* = P<0.05)

Amelio et al., 2017

Conclusions:

- Our results demonstrate that distinct functional profiles of CD4 T-cell responses can be directed against the same pathogen, i.e. *Mtb*, in human populations from different geographic areas.
- Differences in timing and severity of helminth infections, M. tuberculosis strains cirulating and host genetic factors might contribute to this difference in functional CD4 T cell profiles between TZ and SA.
- In TZ, *Mtb*-specific responses are characterized by mixed Th1 and Th2 cytokine production and a highly poly-functional cytokine profile.
- In SA, *Mtb*-specific responses are characterized by CD4 T cells with single IFN-γ and dual IFN-γ/TNF-α co-expression.
- This finding has implications for the diagnostic of clinical and latent TB based on Mtb-specific CD4 T cell cytokine expression as *reduced expression of IL-2 is associated with progression to clinical TB.*

Conclusions:

- Ongoing helminth infections significantly reduced the proportion of volunteers with *Mtb*-specific CD8 T cell responses - echoing findings in virus-specific immunity as *bystander* effect of helminth co-infections.
- Well designed cohort studies will be needed to define the factors driving the distinct functional profiles as well as to determine whether the distinct functional profiles *are associated with variation of the TB pathology and/or response to drug therapy*.
- Type I interferons seem to drive the strong pro-inflammatory response in SA but not TZ volunteers: role of type I interferons in coordinating the phenotype of *Mtb*-specific response needs to be explored.

Acknowledgment:

We would like to thank the study participants in TZ and SA for their willingness to donate blood for these studies.
Tobias Schindler and Julian Rothen: establishing the helminth infection status of the TZ cohort.
Isabelle Zenklusen, Philipp Mächler, Federica Klaus and Jerry Hela facilitated clinical data cleaning.

Service of Immunology and Allergy, Lausanne University Hospital:

Centre hospitalier universitaire vaudois

Patrizia Amelio
Khalid Ohmiti
Song Ding
Matthieu Perreau
Guiseppe Pantaleo

Ifakara Health Institute:

IFAKARA HEALTH INSTITUTE
research | training | services

Francis Mhimbira
Maxmillian Mpina
Anneth Tumbo

South African Tuberculosis Vaccine Initiative:

satvi SOUTH AFRICAN TUBERCULOSIS VACCINE INITIATIVE

Thomas J. Sriba
Adam Penn-Nicholson
Fatoumatta Darboe

Swiss TPH:

Swiss TPH
Swiss Tropical and Public Health Institute
Schweizerisches Tropen- und Public Health-Institut

Hanspeter Marti,
Stefanie Knopp
Beatrice Nickel
Damien Portevin
Klaus Reither
Claudia Daubenberger

Funding:

The research leading to these results has received funding from the [European Community's] Seventh Framework Program ([FP7/2007-2013]) under EC-GA n° [241642] (IDEA).

This work was also supported by Swiss National Science Foundation Grants 320030_173071 and by the Strategic Health Innovation Partnerships (SHIP) Unit of the South African Medical Research Council with funds received from the South African Department of Science and Technology.