Trinity College Dublin
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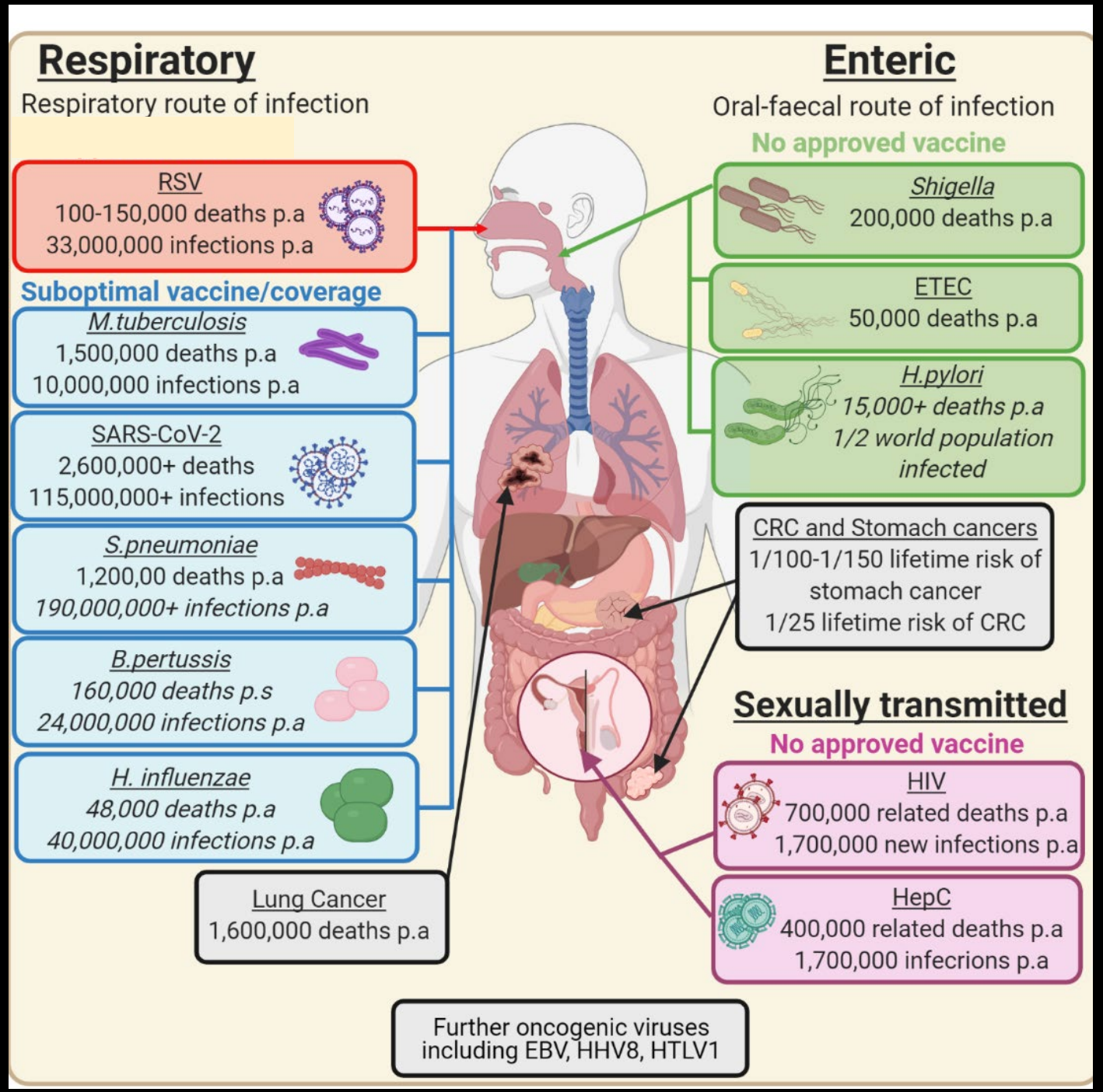
The University of Dublin

Novel adjuvants and mucosal vaccination strategies

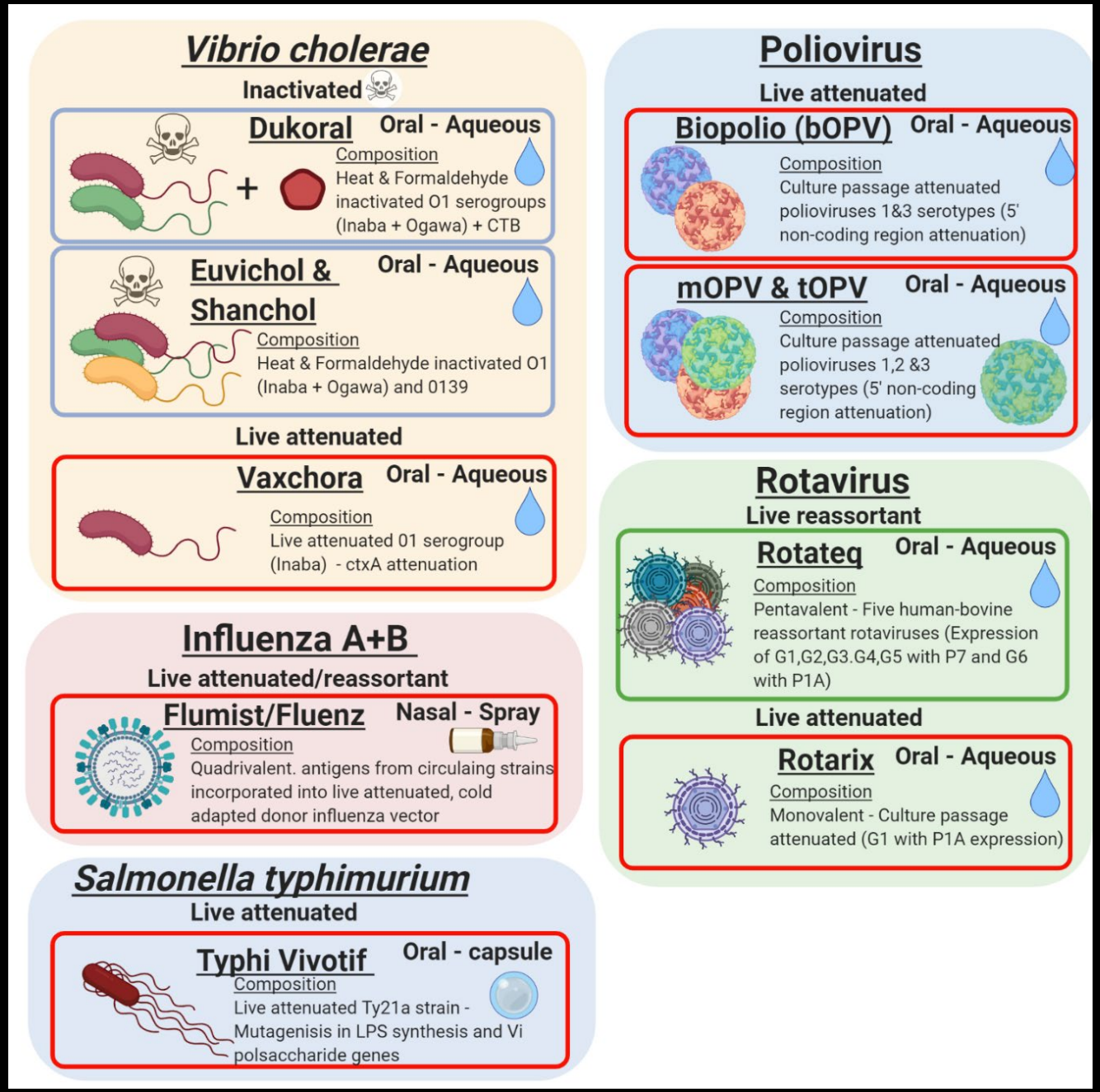
Ed Lavelle

25/3/2025



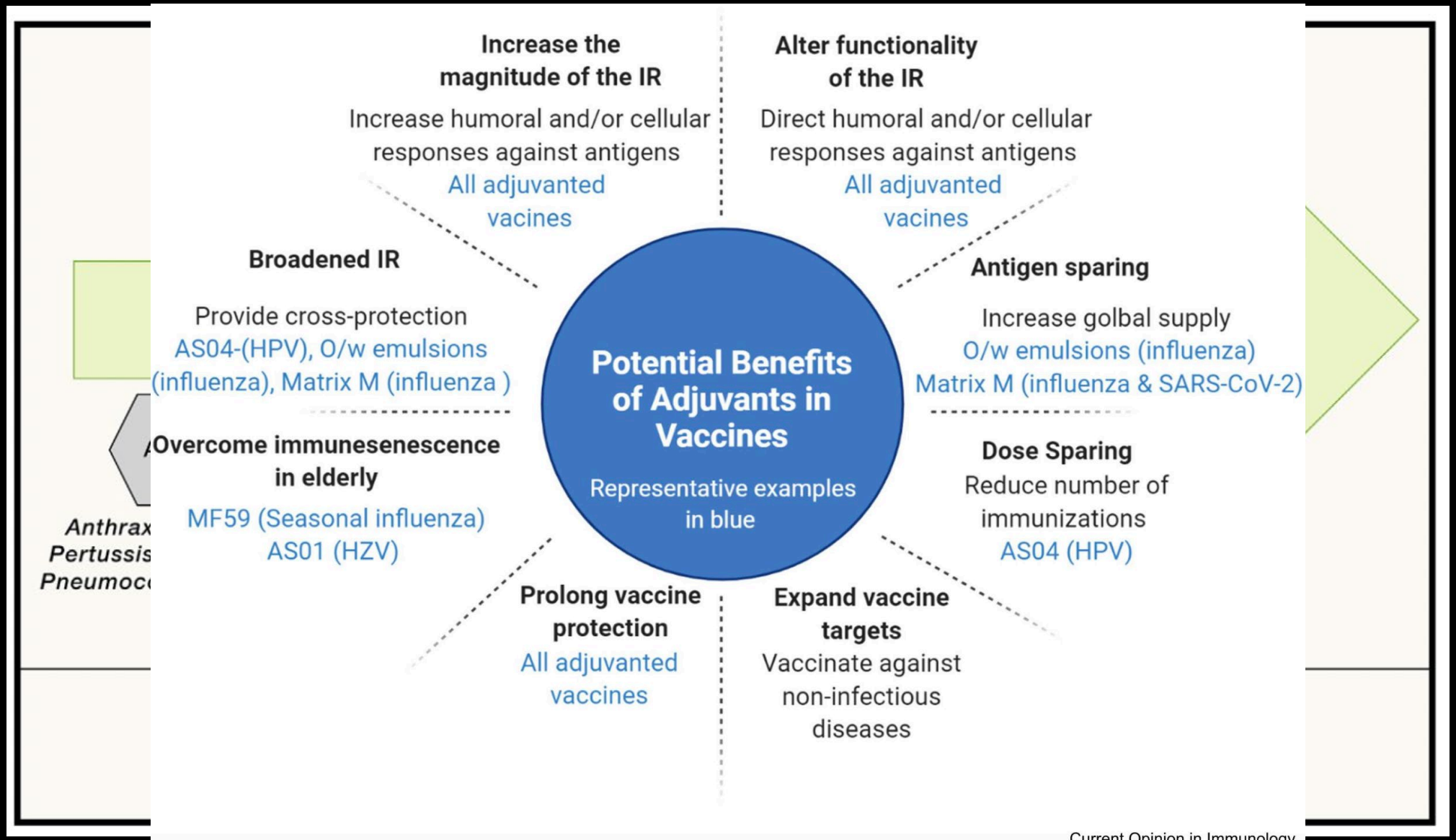
Lavelle and Ward. *Nature Rev Immunol.* 2022.
doi: 10.1038/s41577-021-00583-2.

Mucosal vaccines in clinical use



Lavelle and Ward. *Nature Rev Immunol.* 2022. doi: 10.1038/s41577-021-00583-2.

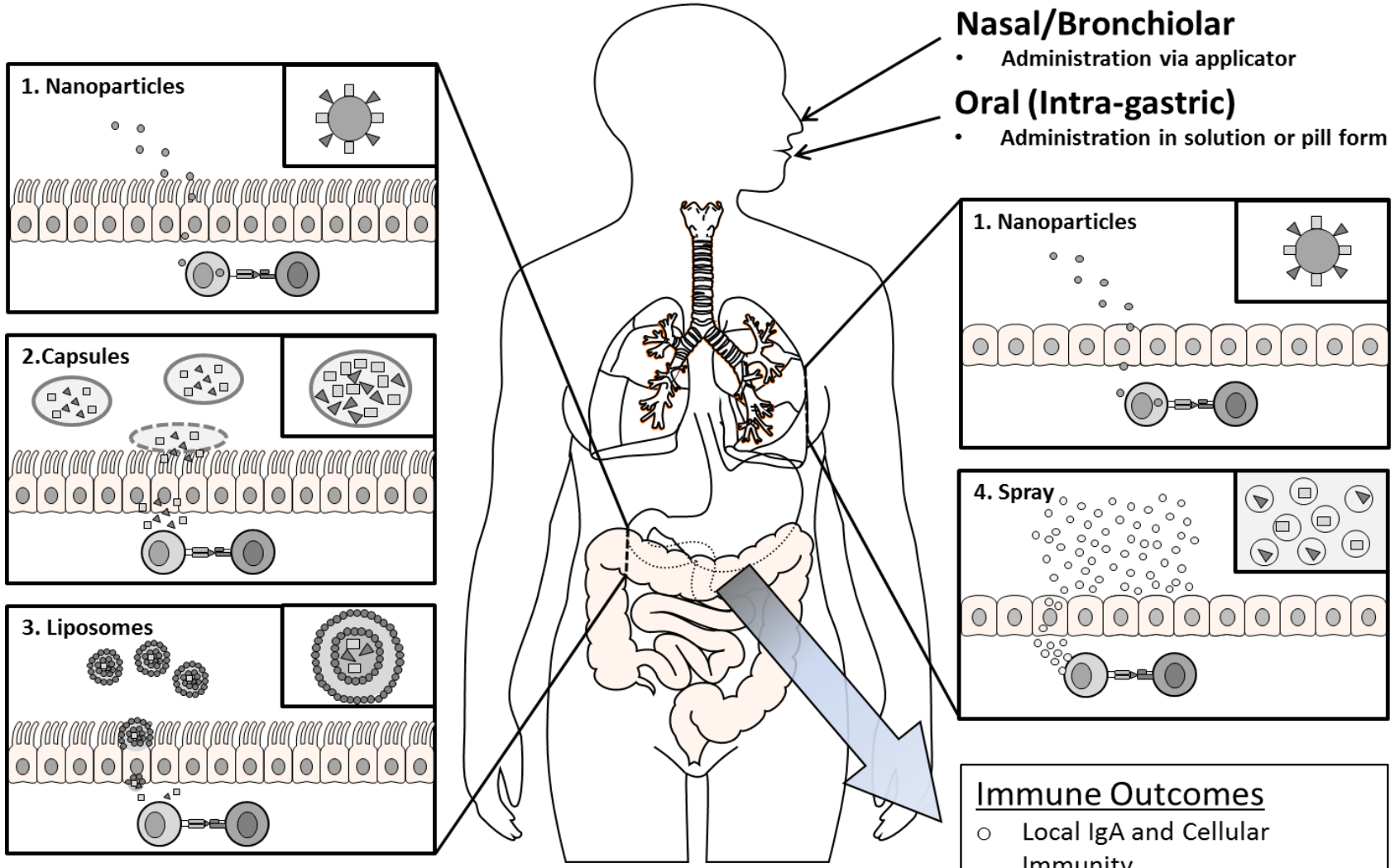
Timeline of vaccine adjuvant development

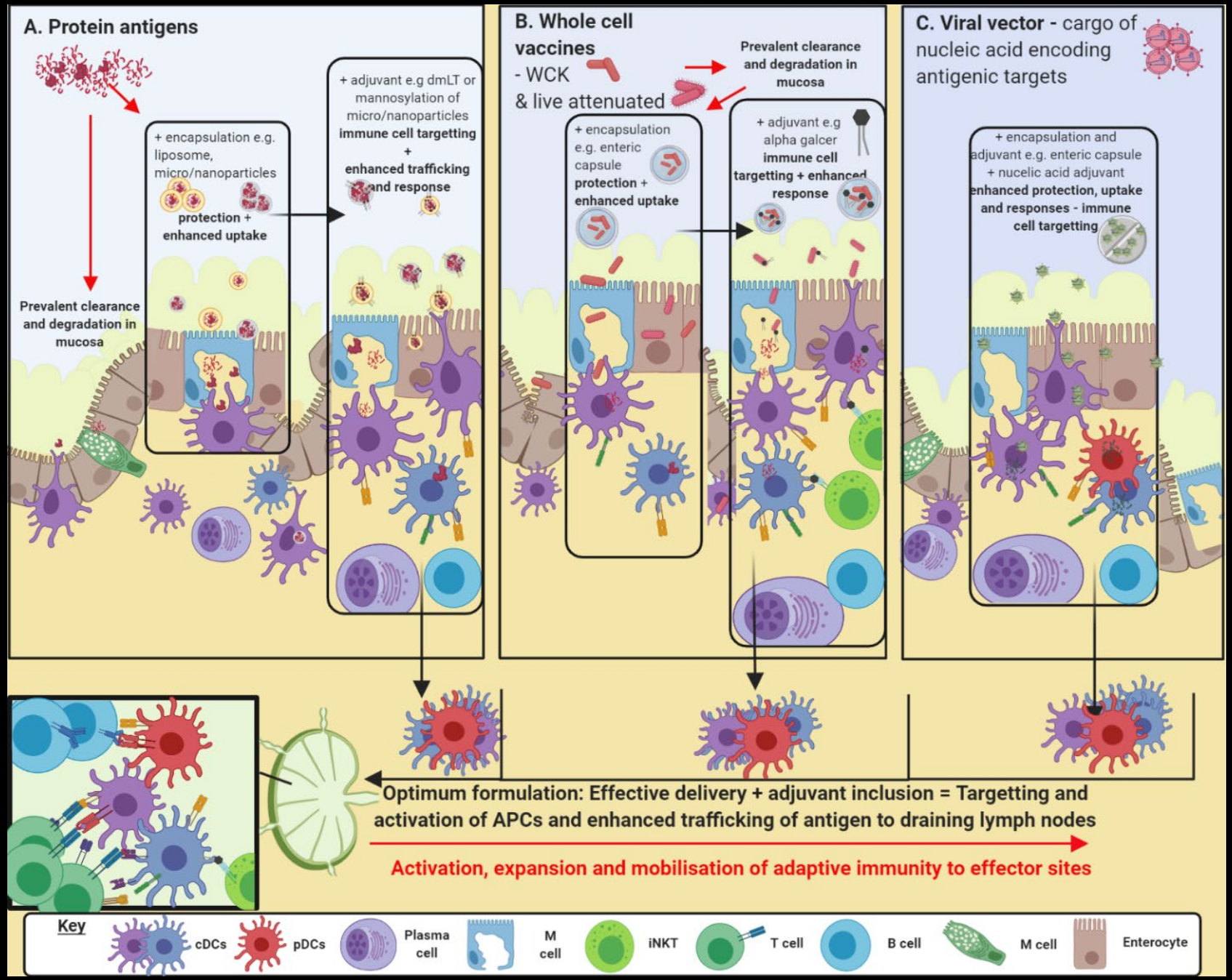


Lavelle & McEntee, *Immunity,* 2024

Mucosal Vaccination

Targets the key site of infection, advantages for developing countries; less requirement for trained personnel



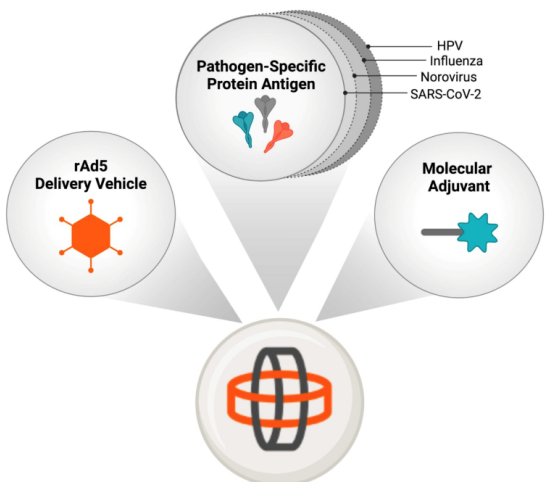


Lavelle and Ward. *Nature Rev Immunol.* 2022. doi: 10.1038/s41577-021-00583-2.

Revolutionizing Immunizations with VAAST®

Vaxart has developed a unique modular vaccine platform called Vector-Adjuvant-Antigen Standardized Technology (VAAST).

Vaxart's Proprietary VAAST Platform: Vector-Adjuvant-Antigen Standardized Technology (VAAST)

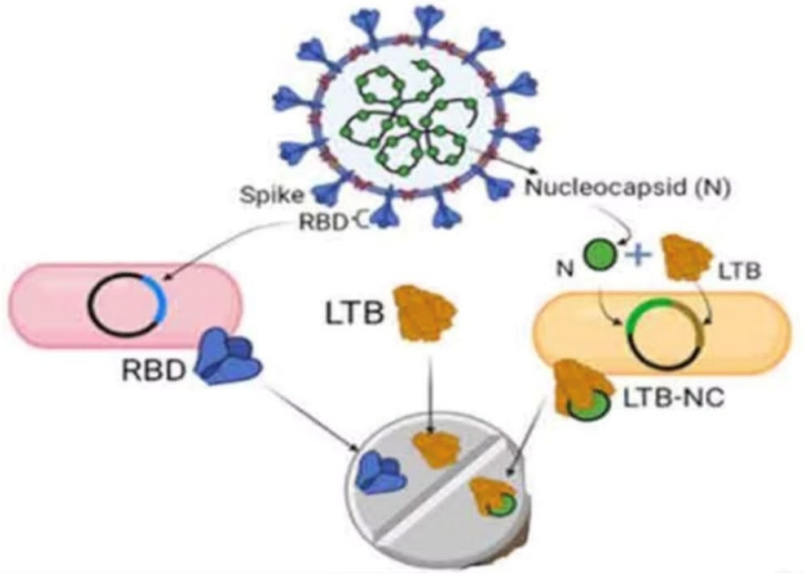


VAAST combines three key components:

1. **Recombinant Adenovirus Type 5 (rAd5):** non-replicating recombinant delivery vector
2. **Antigens:** viral proteins that stimulate the immune system to recognize the targeted pathogen
3. **Molecular Adjuvant:** enhances the immune response, making the vaccine even more effective

MigVax

- Oral Tablet COVID-19 Subunit vaccine
- Dissolves on the tongue.
- Stable at room temperature for 2 months.



Vaccine 40 (2022) 1098–1107

Contents lists available at ScienceDirect

Vaccine

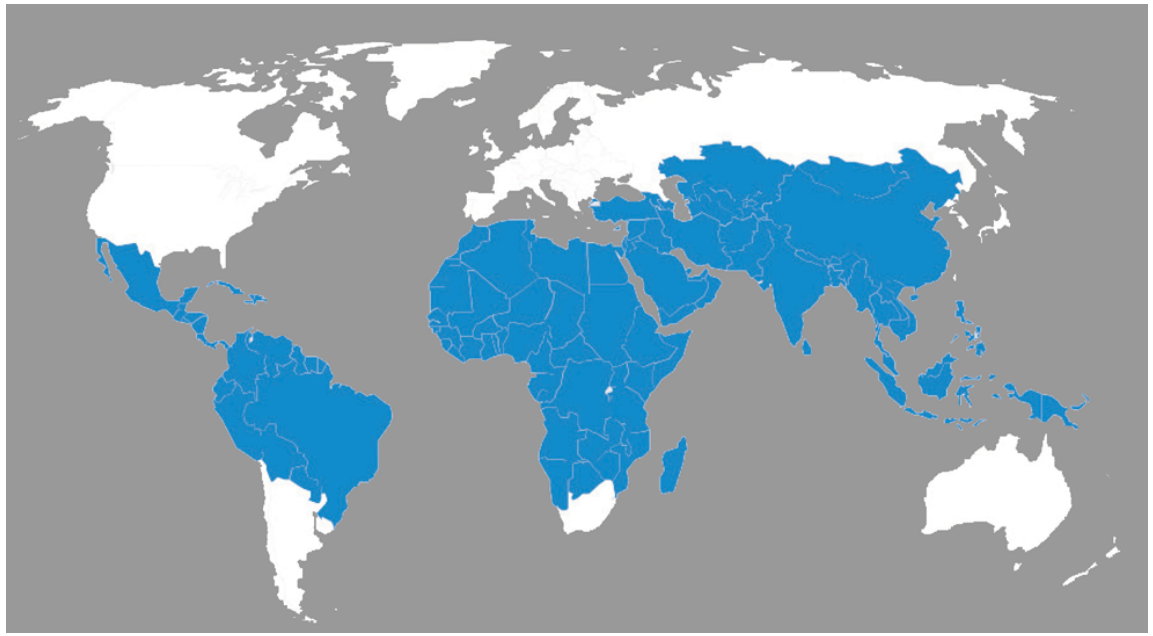
journal homepage: www.elsevier.com/locate/vaccine

Oral subunit SARS-CoV-2 vaccine induces systemic neutralizing IgG, IgA and cellular immune responses and can boost neutralizing antibody responses primed by an injected vaccine

Jacob Pitcovski [a,c], Nady Gruzdev [a], Anna Abzach [a], Chen Katz [a], Ran Ben-Adiva [a], Michal Brand-Shwartz [a], Itamar Yadid [a,c], Einav Ratzon-Ashkenazi [b], Ken Emquies [a], Hadasa Israeli [a], Hadar Haviv [a], Irena Rapoport [a], Itai Bloch [a], Roy Shadmon [b], Zohar Eitan [b], Dalia Eliahu [a], Talia Hilel [a], Morris Laster [b], Sigal Kremer-Tal [b], Tamara Byk-Tennenbaum [b], Ehud Shahar [a,c,*]

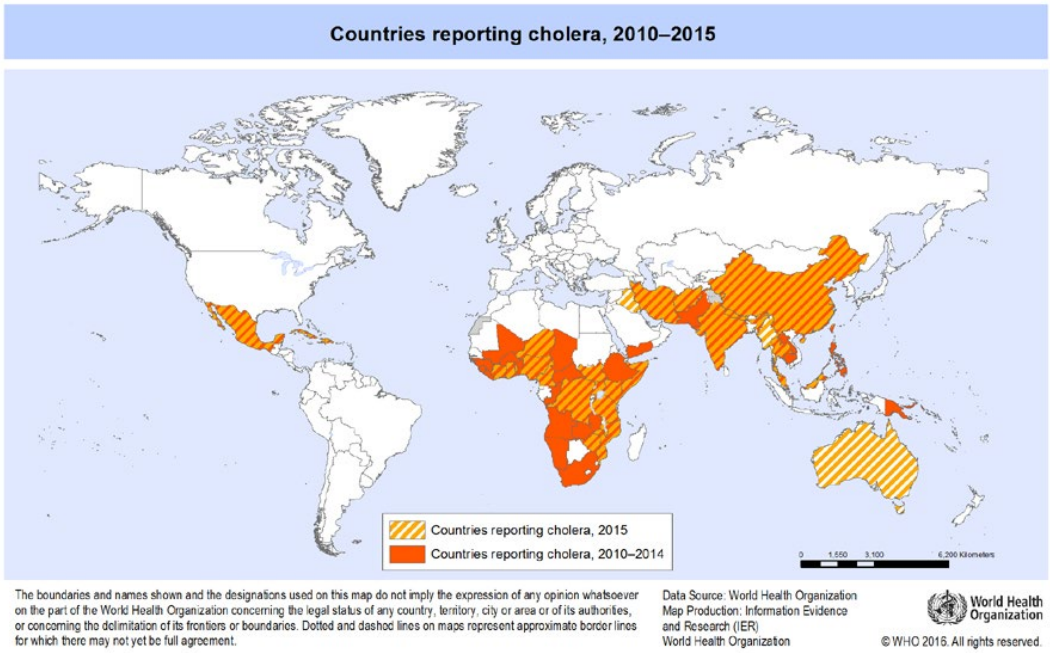
[a] MIGAL Research Institute in the Galilee, Kiryat Shmona, Israel
[b] MigVax Ltd., Israel
[c] Tel-Hai Academic College, Upper Galilee, Israel

ETEC infections



Bio Ventures for Global Health

Cholera



http://www.who.int/gho/epidemic_diseases/cholera/epidemics/en/

No vaccine

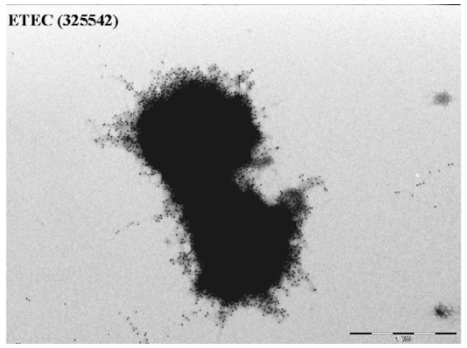
Oral cholera vaccines need to be improved

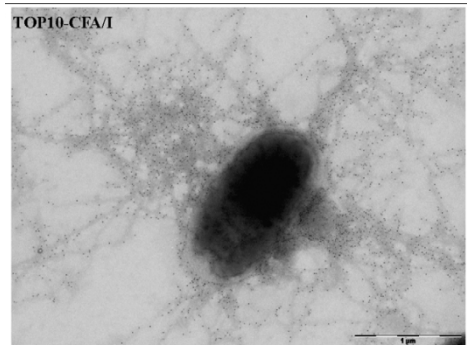
Particularly in developed countries, ***Helicobacter pylori*** causes chronic infections that can lead to peptic ulcers and may be a risk for gastric cancer development → No vaccine

Strategies to enhance oral vaccine immunogenicity

✓Increase the antigen load on whole cell killed bacteria

Recombinant *E. coli* over-expressing CFA/I (JT-49 *E. coli*)





Tobias et al., 2008

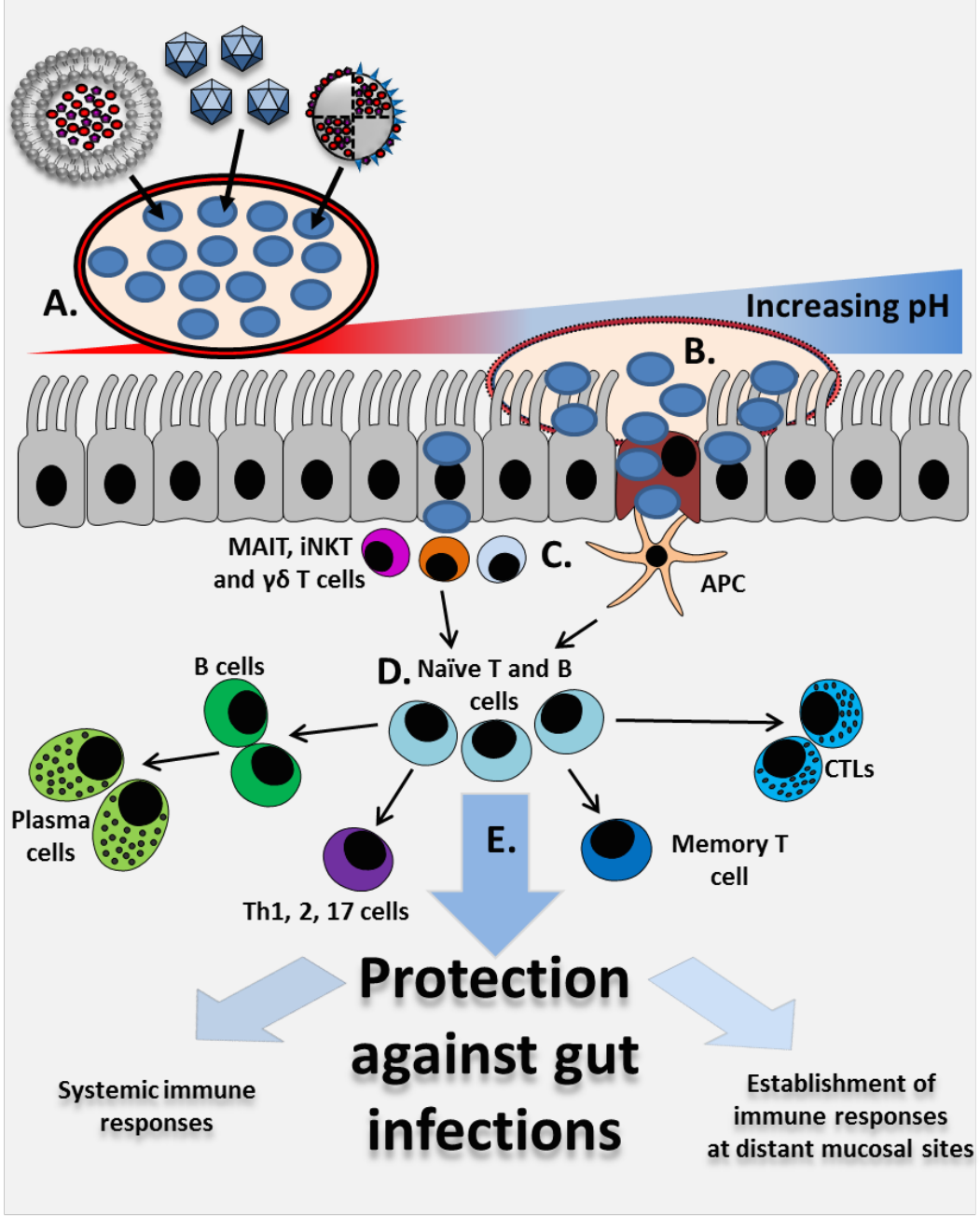
The strain was shown to be safe, well tolerated and immunogenic during trials in Swedish volunteers

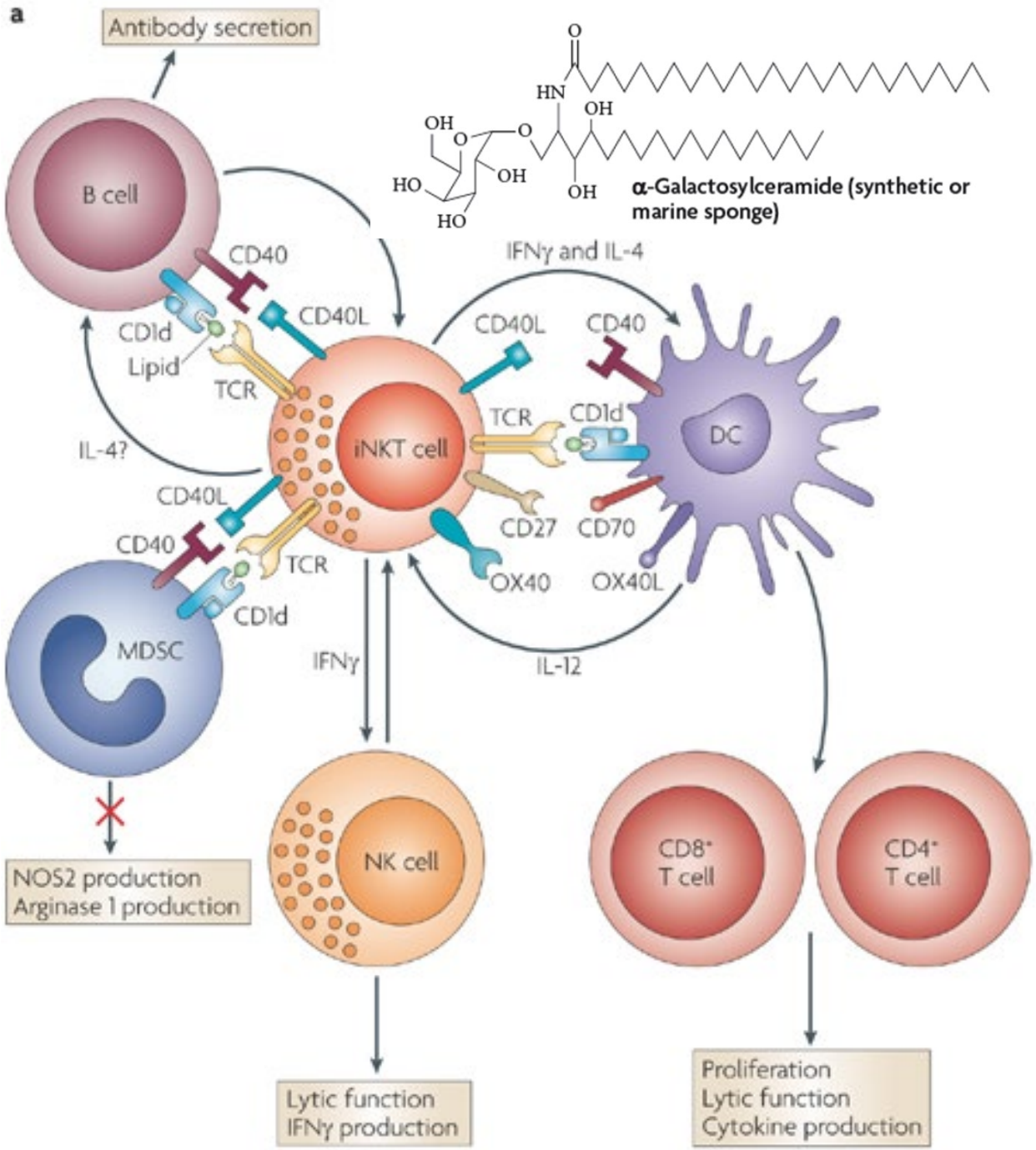
✓Identification of effective orally active adjuvants

Cholera toxin is the gold standard in animal models but is too toxic to be used in humans

Mutated CT (mmCT) or ETEC heat-labile toxin (dmLT) - currently in clinical trials

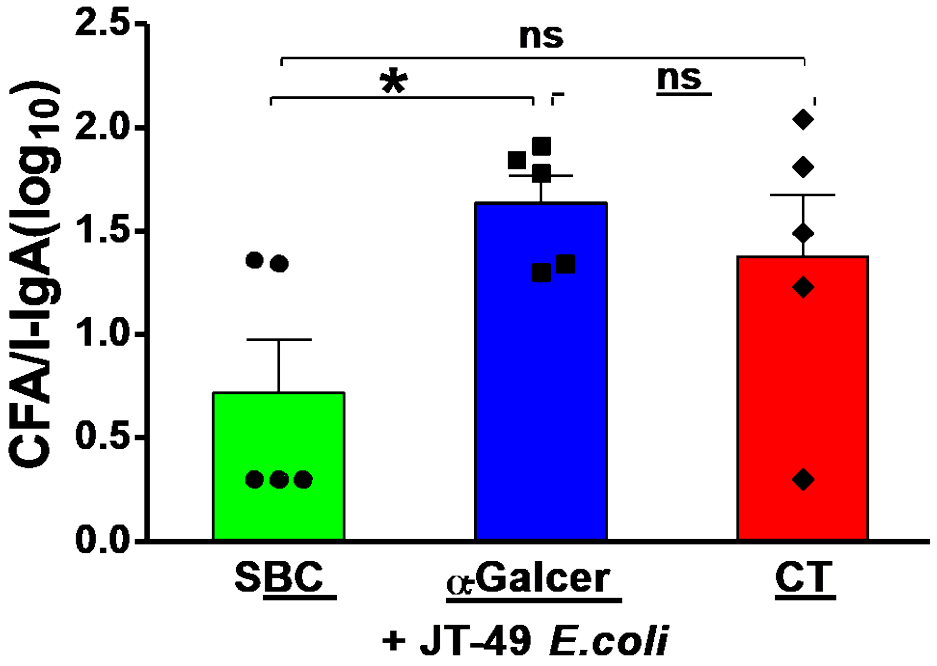
Additional safe and effective adjuvants are required

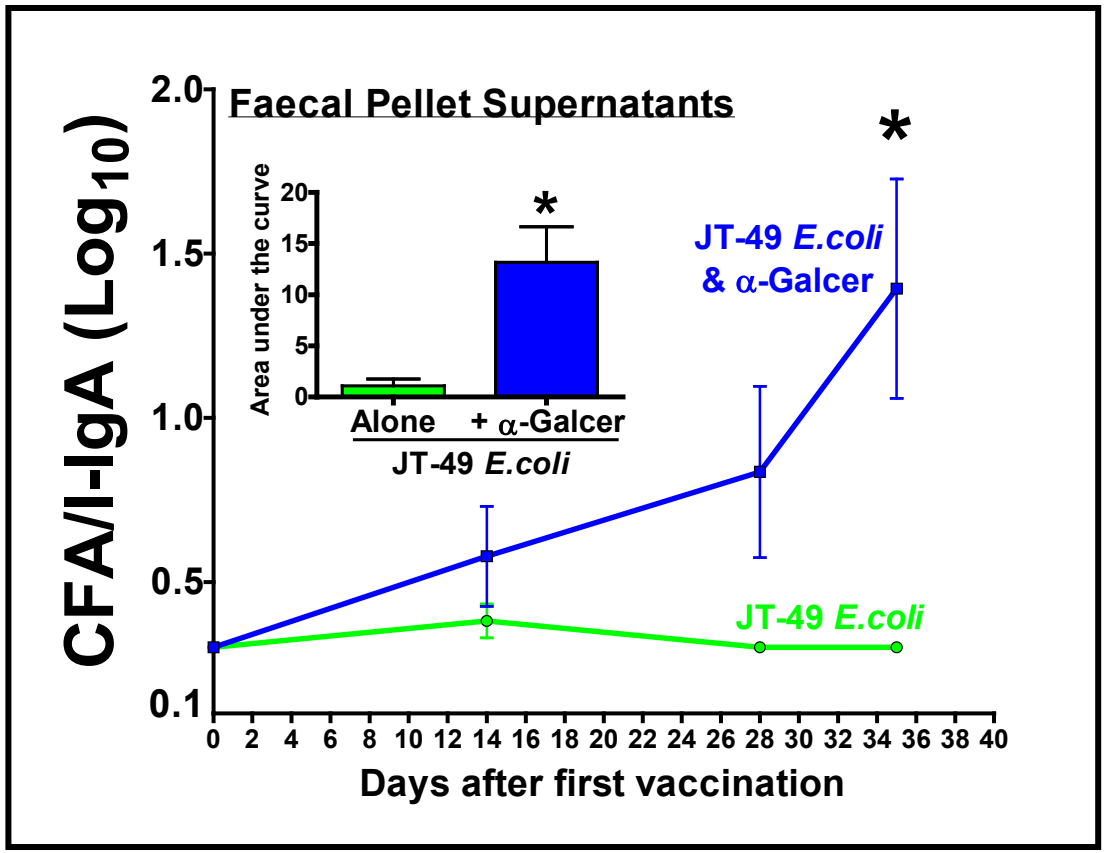


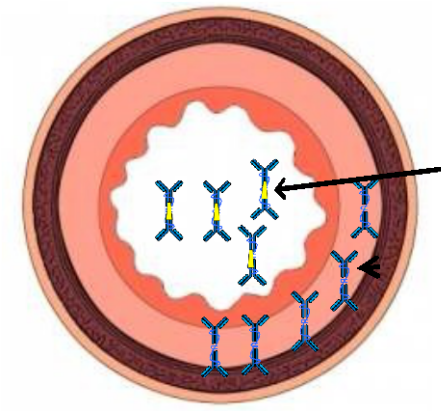


doi: 10.1016/j.addr.2015.03.007

α-GalCer is an effective adjuvant for oral vaccination with ETEC antigen



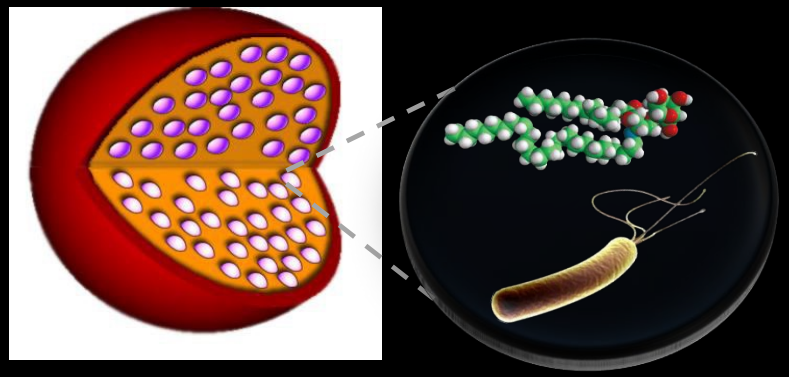




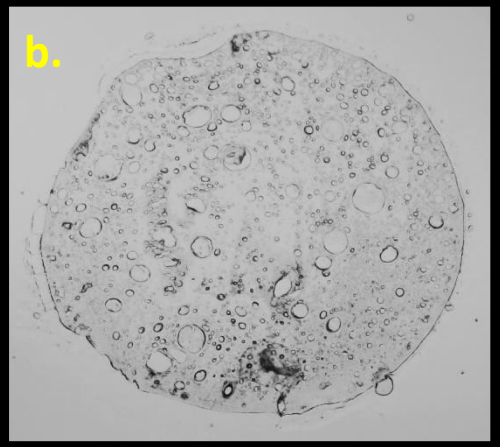
Readouts of Oral Vaccine Efficacy

- Faecal Pellet IgA
- Intestinal Tissue IgA (following perfusion)
- Intestinal Wash IgA

a.

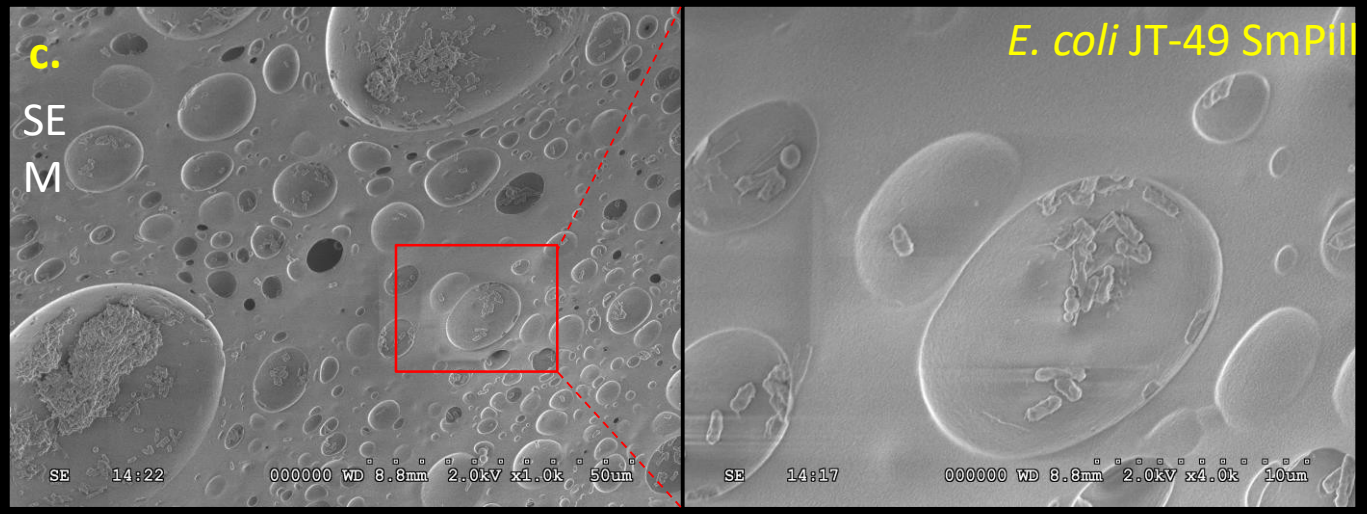


b.



c.

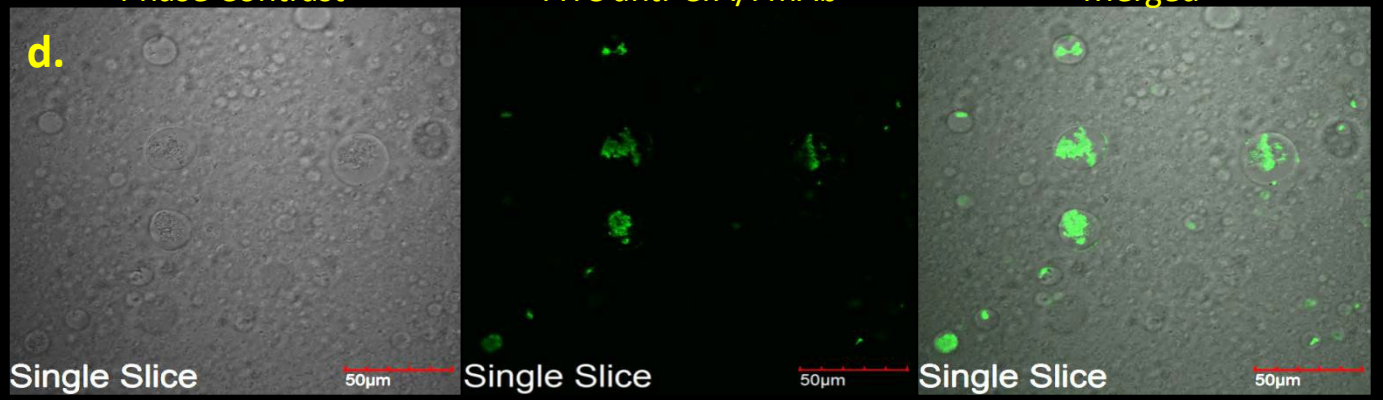
SE
M



E. coli JT-49 SmPIII

Phase Contrast | FITC anti-CFA/I mAb | Merged

d.



Oral cholera vaccines

3 licensed oral cholera vaccines (e.g. Dukoral®)

- Challenges
  - Short-term protection
  - Less efficient in endemic populations
  - Several whole cell killed *V. cholerae* strains

Unicef predicts fresh outbreak of deadly cholera in Yemen

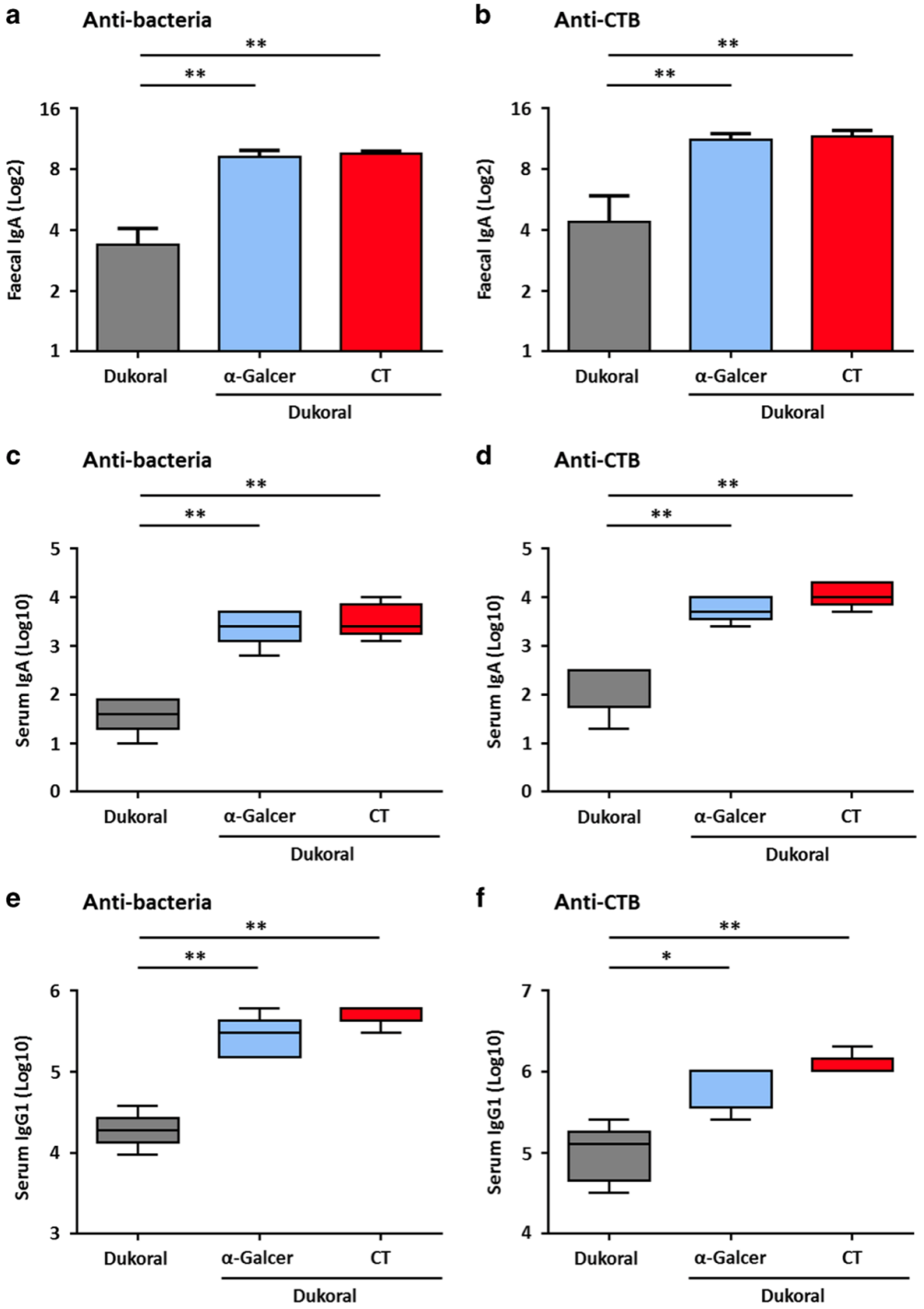
Official warns disease that hit more than 1m children in 2017 will return within months

▲ Yemeni children present documents to receive food rations provided by a local charity in Sana'a, Yemen. Photograph: Hani Mohammed/AP

Yemen is likely to be hit by another outbreak of deadly cholera within months, Unicef's Middle East director has warned on the eve of the third anniversary of the country's civil war.

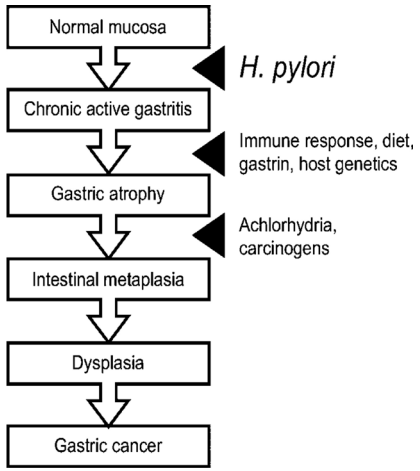
The Guardian, March 2018

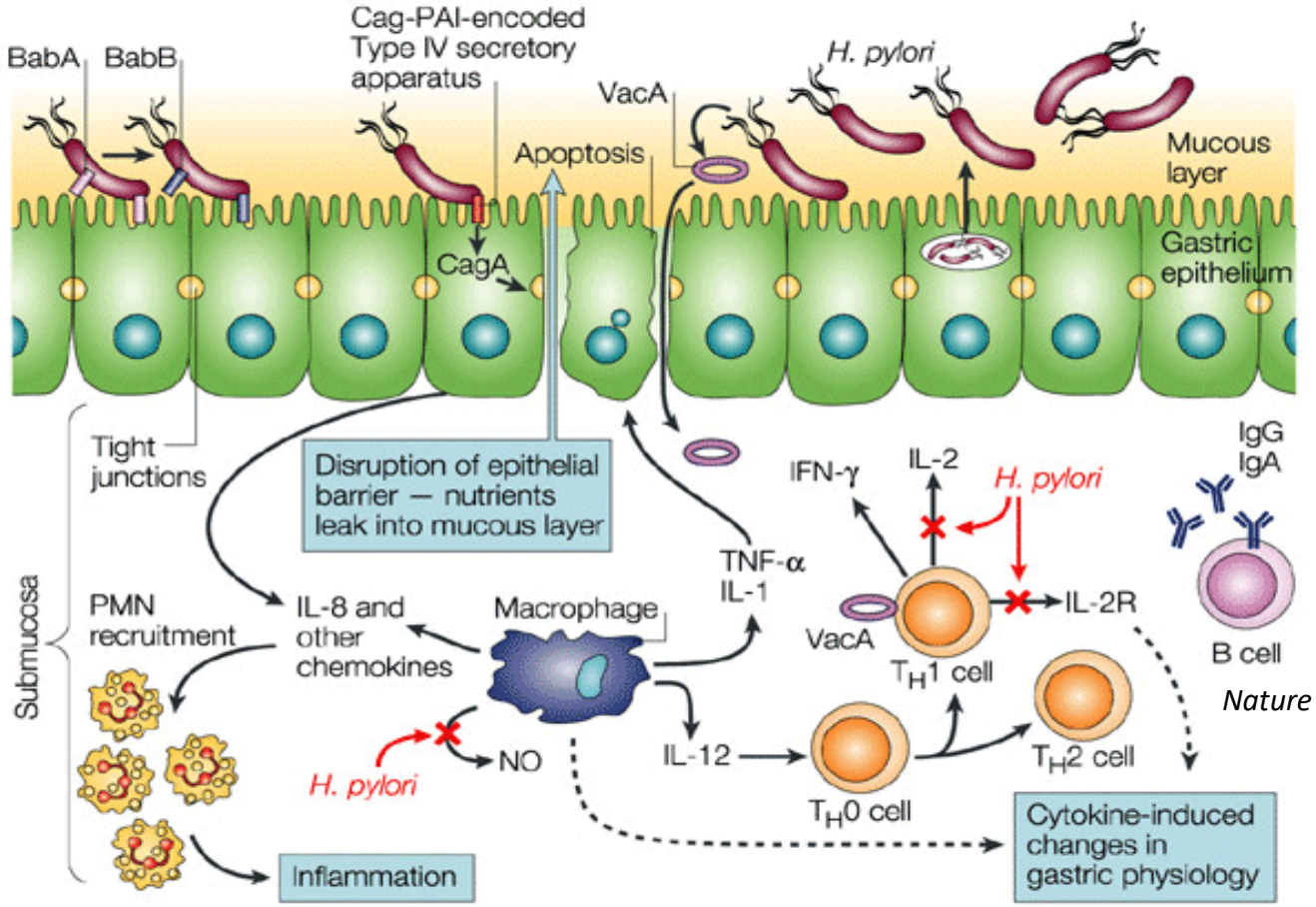
α-GalCer enhances antigen-specific faecal IgA, serum IgA and IgG1 in female C57BL/6 mice



Davitt, Longet et al, 2019. *Mucosal Immunol*
doi: 10.1038/s41385-019-0159-z

Helicobacter pylori pathogenesis





Denise M. Monack et al.
Nature Reviews Microbiology **2**, 747-765

Protection against Experimental *Helicobacter pylori* Infection after Immunization with Inactivated *H. pylori* Whole-Cell Vaccines

S. Raghavan, M. Hjulström, J. Holmgren, and A.-M. Svennerholm*

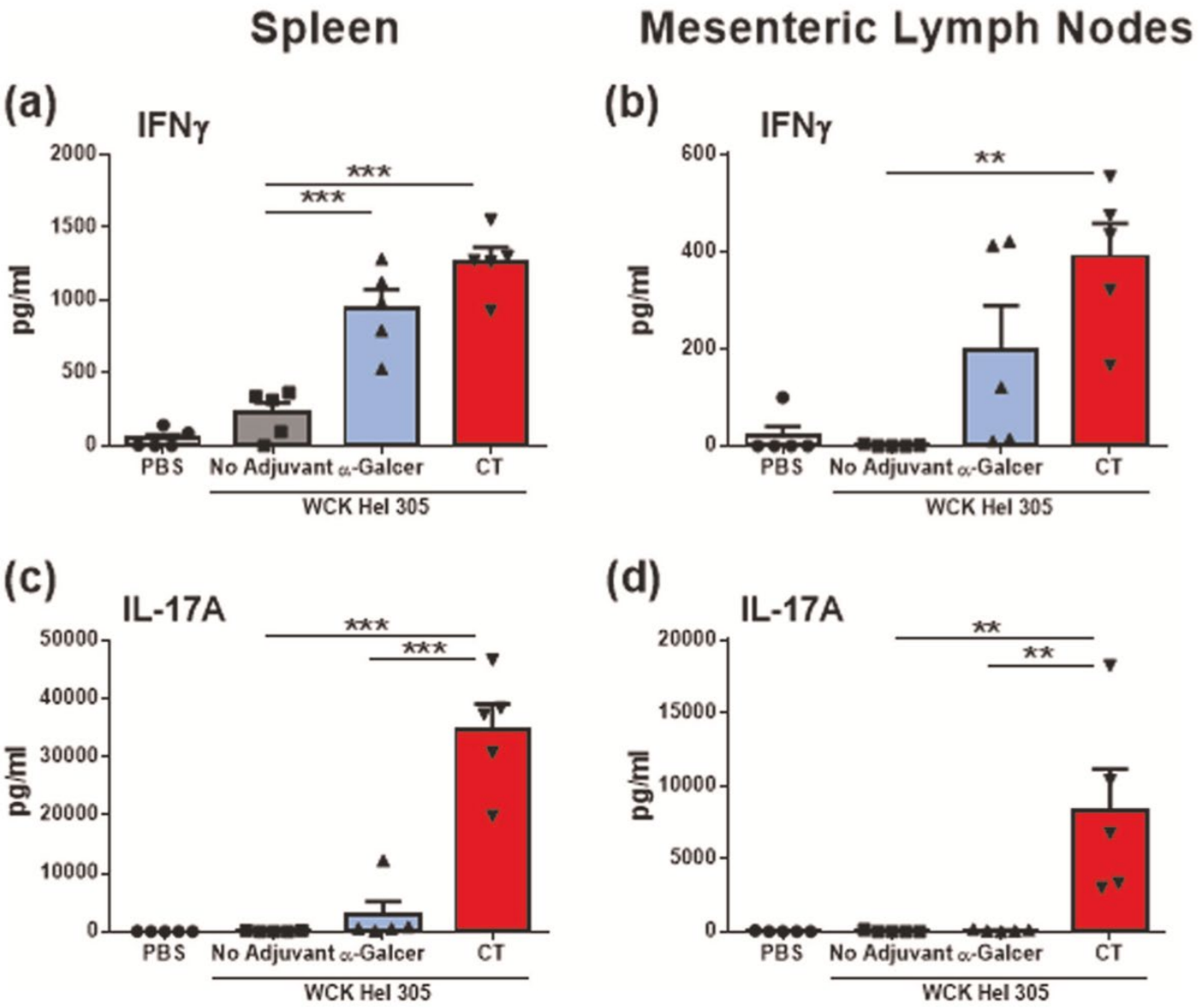
Department of Medical Microbiology and Immunology and Göteborg University Vaccine Research Institute (GUVAX), Göteborg University, S 41346 Göteborg, Sweden

Nature Reviews | Microbiology

> Formaldehyde-killed *H. pylori* Hel-305 ($CagA^+$ $VacA^+$)

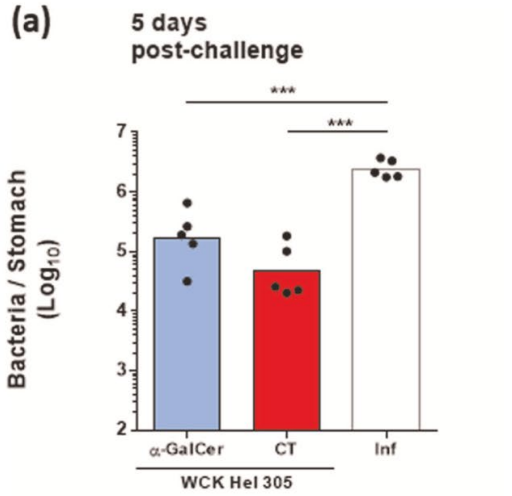
Raghavan *et al* IAI 2002
Sjökvist Ottsjö *et al* IAI 2013

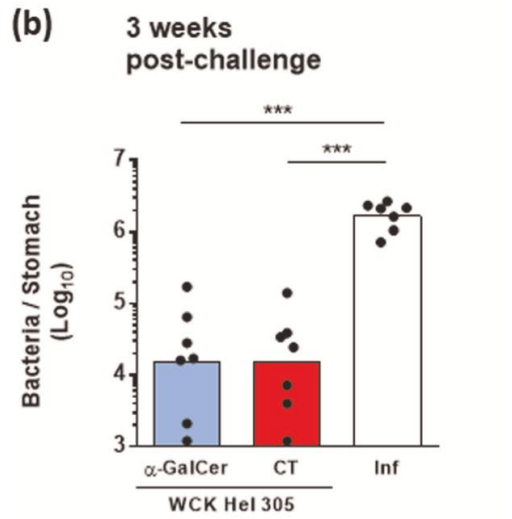
Oral α-GalCer enhances antigen-specific Th1 responses

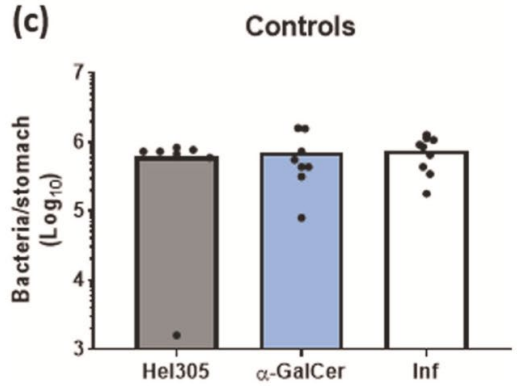


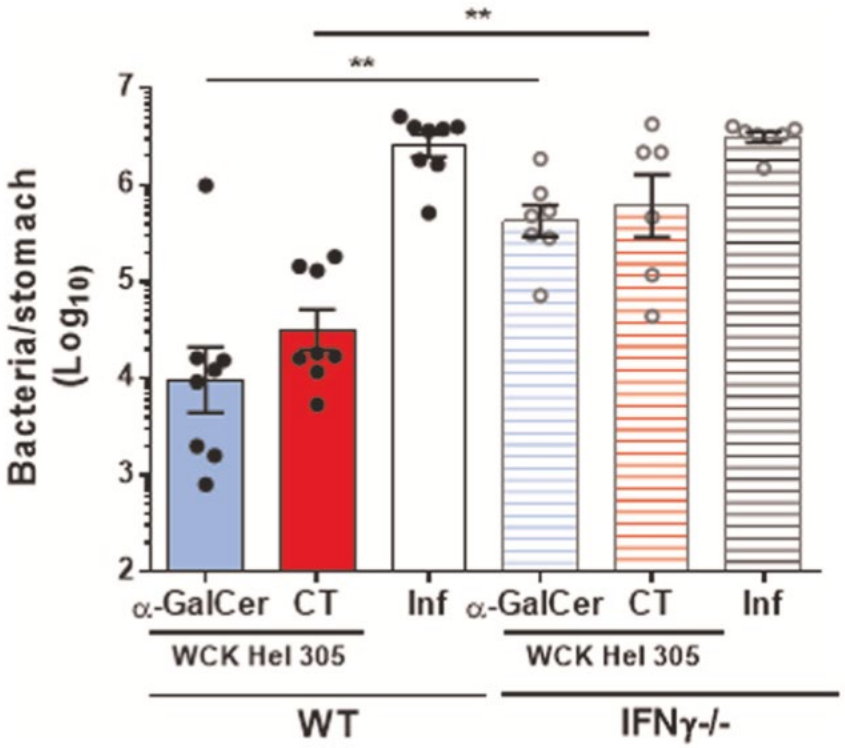
Longet et al NPJ Vaccines 2019.
doi: 10.1038/s41541-019-0139-z

Vaccine induced Th1 responses are protective against H. pylori challenge



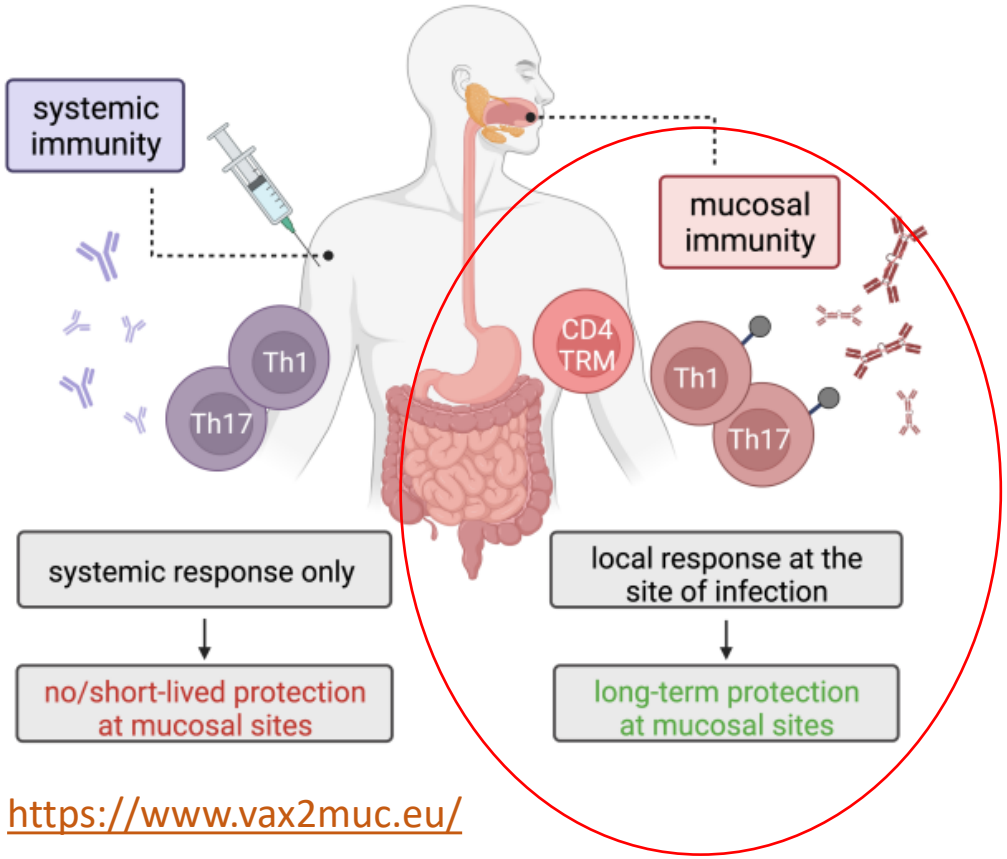






Longet et al NPJ Vaccines 2019.
doi: 10.1038/s41541-019-0139-z

Vax2muc – Vaccination against *H. pylori*



https://www.vax2muc.eu/

npj | Vaccines
www.nature.com/npjvaccines

ARTICLE OPEN

An oral alpha-galactosylceramide adjuvanted *Helicobacter pylori* vaccine induces protective IL-1R- and IL-17R-dependent Th1 responses

Stephanie Longet[1,5], Aine Abautret-Daly[1,5], Christopher J. H. Davitt[1], Craig P. McEntee[1], Vincenzo Aversa[2], Monica Rosa[2], Ivan S. Coulter[2], Jan Holmgren[3], Sukanya Raghavan[3,6*] and Ed C. Lavelle[1,4,6*]

Protection Against *Helicobacter pylori* Infection Following Immunization Is IL-12-Dependent and Mediated by Th1 Cells[1]

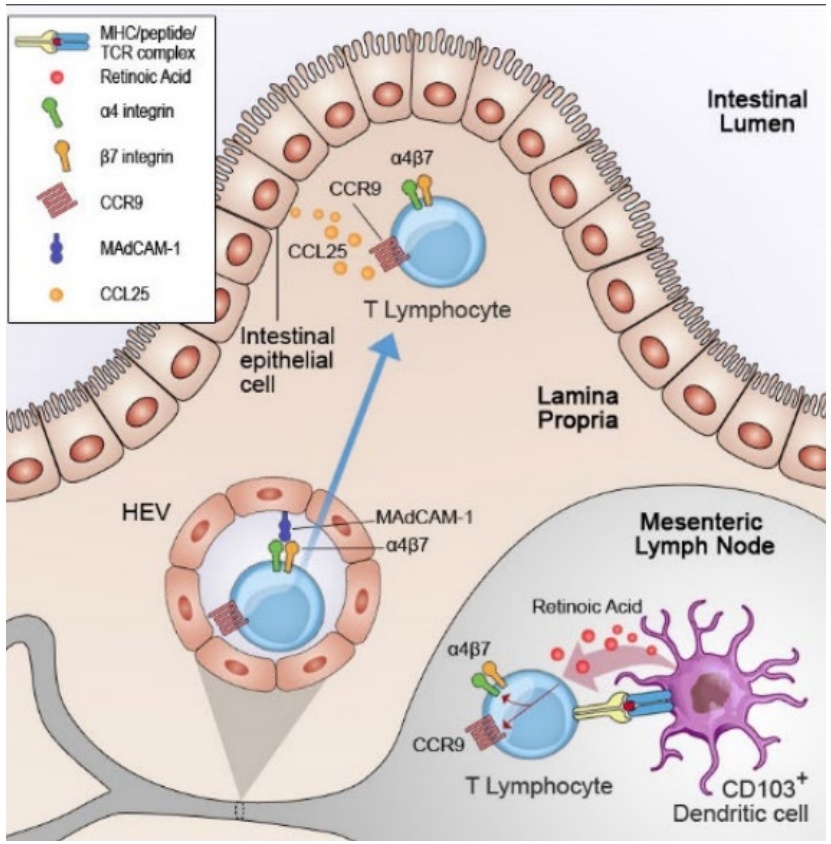
Ali A. Akhiani,* Jacques Pappo,† Zita Kabok,† Karin Schön,* Wei Gao,† Lennart E. Franzén,‡ and Nils Lycke*

frontiers in Immunology
ORIGINAL RESEARCH
published: 17 May 2019
doi: 10.3389/fimmu.2019.01115

Gastric Subserous Vaccination With *Helicobacter pylori* Vaccine: An Attempt to Establish Tissue-Resident CD4+ Memory T Cells and Induce Prolonged Protection

Wei Liu[1,2], Zhiqin Zeng[1,2], Shuanghui Luo[1,2], Chupeng Hu[1,2], Ningyin Xu[1,2], An Huang[1,2], Lufeng Zheng[1,2], Eric J. Sundberg[3,4], Tao Xi[1,2] and Yingying Xing[1,2]**

ATRA analogs to promote gastrointestinal tissue resident immunity?



Bono, M., Tejon, G., Flores-Santibañez, F., Fernandez, D., Rosemblatt, M. and Sauma, D. (2016). Retinoic Acid as a Modulator of T Cell Immunity. *Nutrients*, [online] 8(6), p.349. doi:https://doi.org/10.3390/nu8060349.

Human gastric epithelial cells contribute to gastric immune regulation by providing retinoic acid to dendritic cells

D Bimczok[1], JY Kao[2], M Zhang[2], S Cochrun[1], P Mannon[1], S Peter[1], CM Wilcox[1], KE Mönkemüller[1], PR Harris[3], JM Grams[4], RD Stahl[4], PD Smith[1,5] and LE Smythies[1]

GASTROENTEROLOGY 2000;119:109–118

Gastric Mucosal $\alpha_4\beta_7$-Integrin–Positive CD4 T Lymphocytes and Immune Protection Against *Helicobacter* Infection in Mice

MURIELLE MICHETTI,* CIARÁN P. KELLY,* JEAN-PIERRE KRAEHENBUHL,‡ HANIFA BOUZOURENE,§ and PIERRE MICHETTI*

*Division of Gastroenterology, Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, Massachusetts; ‡Swiss Institute for Experimental Cancer Research and Institute of Biochemistry, University of Lausanne, Epalinges, Switzerland; and §Pathology Institute, University of Lausanne, Lausanne, Switzerland

INFECTION AND IMMUNITY, Feb. 2004, p. 1004–1009 Vol. 72, No. 2
0019-9567/04/$08.00+0 DOI: 10.1128/IAI.72.2.1004–1009.2004

Mucosal Vaccination Increases Endothelial Expression of Mucosal Addressin Cell Adhesion Molecule 1 in the Human Gastrointestinal Tract

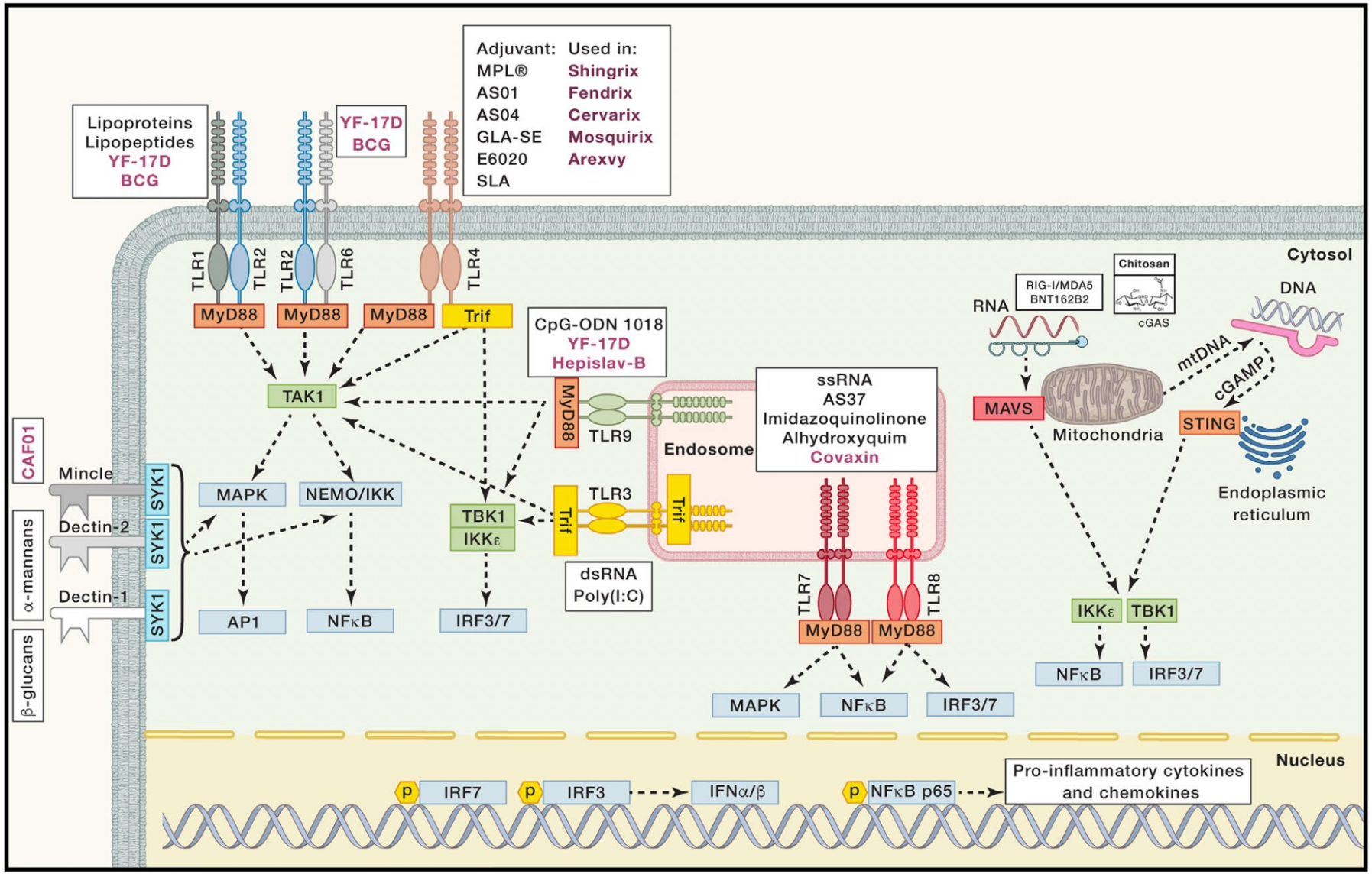
Catharina Lindholm,[1]* Andrew Naylor,[2] Eva-Liz Johansson,[1] and Marianne Quiding-Järbrink[1]

Department of Medical Microbiology and Immunology and Göteborg University Vaccine Research Center[1] and Department of Physiology, Sahlgrenska Academy at Göteborg University,[2] Göteborg, Sweden

Received 7 July 2003/Returned for modification 2 September 2003/Accepted 3 November 2003

Resolving adjuvant targets and mode of action is essential

- How are the vaccine target receptors and target cells regulated: influence of age, sex etc?
- Are the effects dependent on genetics, hormones, microbiome?
- Do we need to optimize mucosal vaccines for different groups?



Lavelle & McEntee, *Immunity*, 2024

Acknowledgements

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European Commission
Horizon Europe
2021-2027

sfi Science Foundation Ireland

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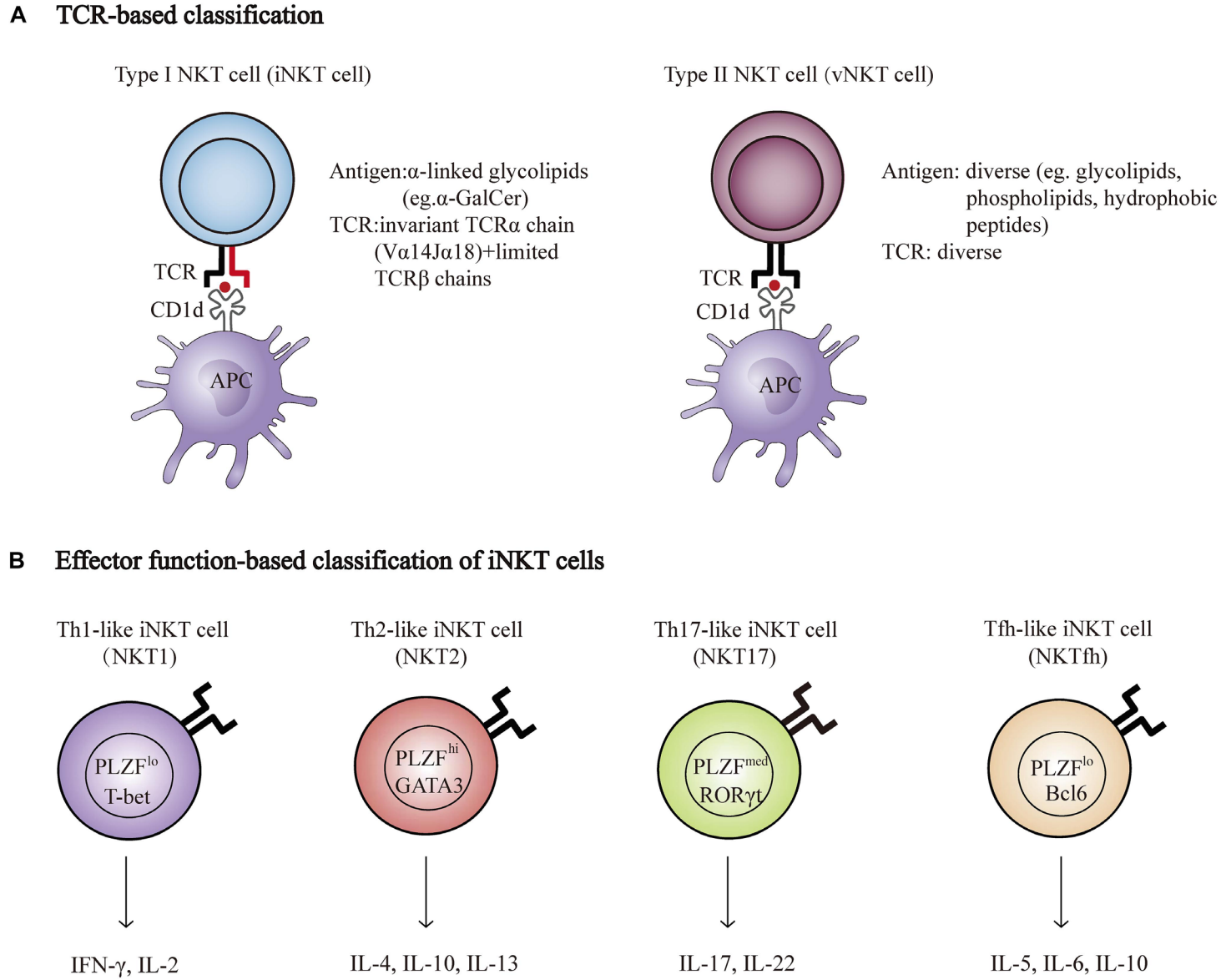
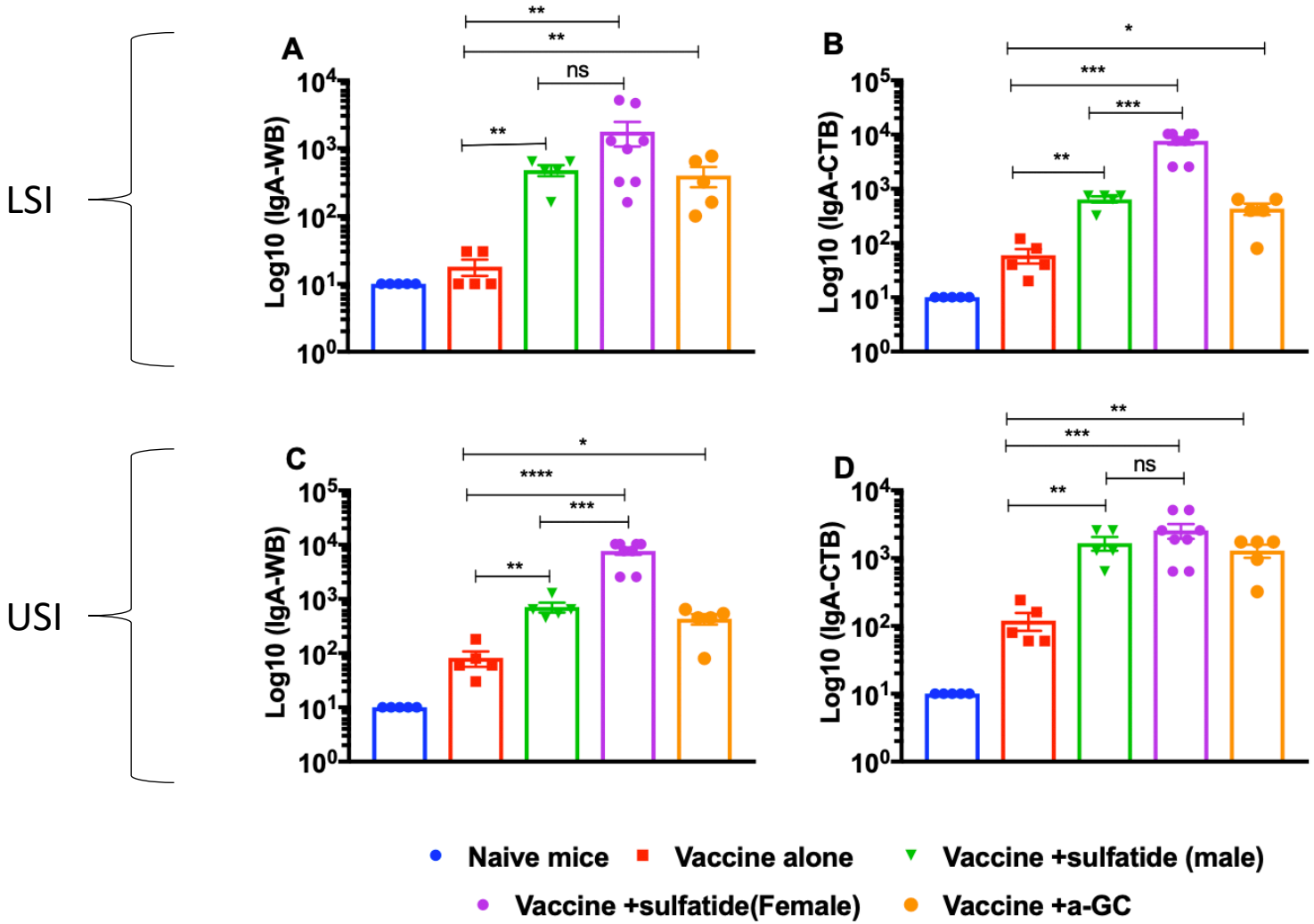


Cui and Wan. *Front. Cell. Neurosci.*, https://doi.org/10.3389/fncel.2019.00245

Intestinal tissues



All groups were males with the exception of vaccine + sulfatide (females)