

Correlates of Protection against Enterotoxigenic *Escherichia coli*

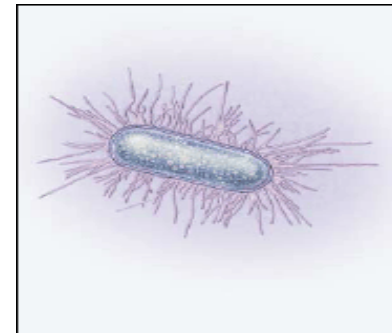
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Correlates of enteric vaccine induced protection
Fondation Merieux, Annecy
22 March, 2016

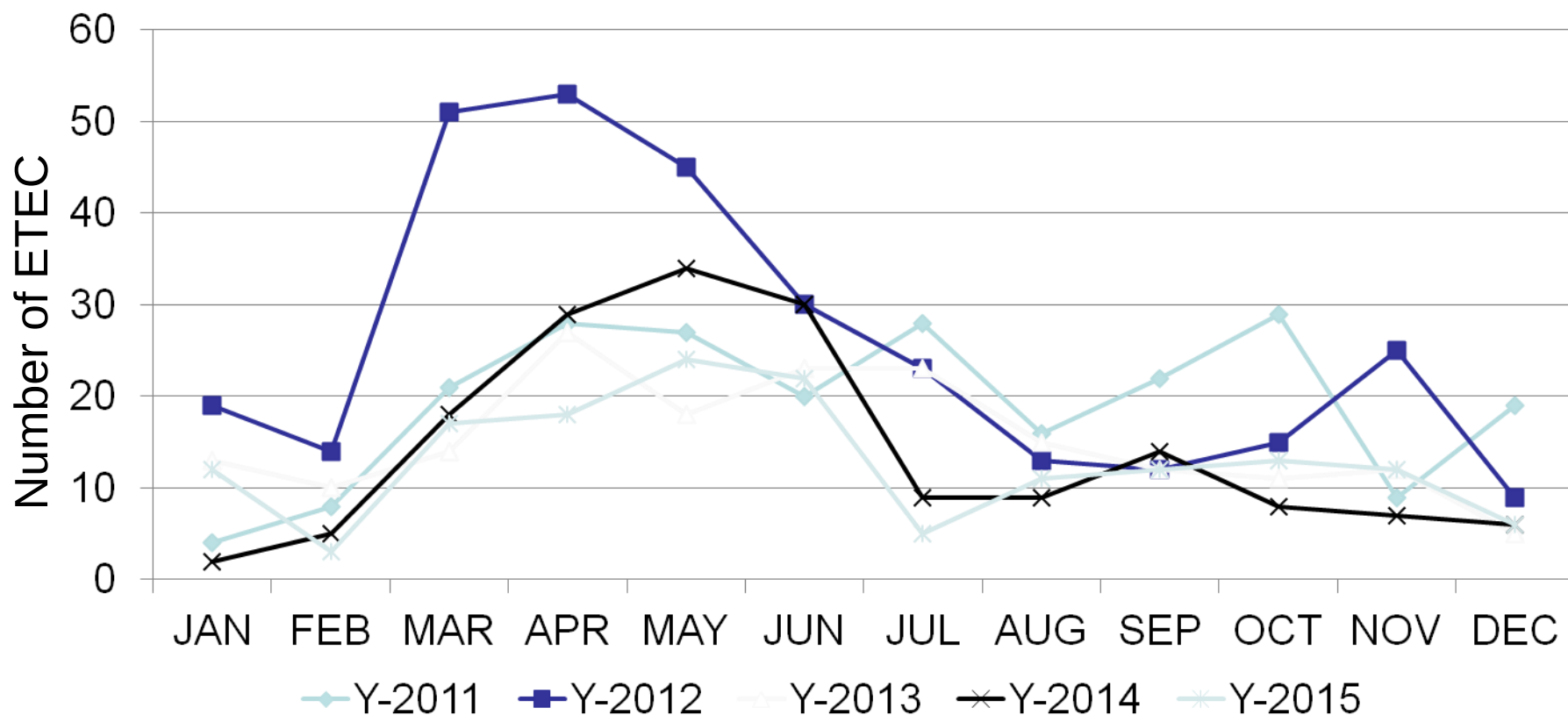
Importance of enterotoxigenic *E. coli* (ETEC) in children in developing countries

- In Bangladesh, acute dehydrating diarrhea is common and epidemics seen at least two times every year and additionally peaks during natural disasters
- ETEC is the most common cause of bacterial diarrhea in children ≤ 3 years (10- 20% of all cases)
- Repeated ETEC diarrheas can cause **malnutrition, growth retardation and stunting**



E. coli

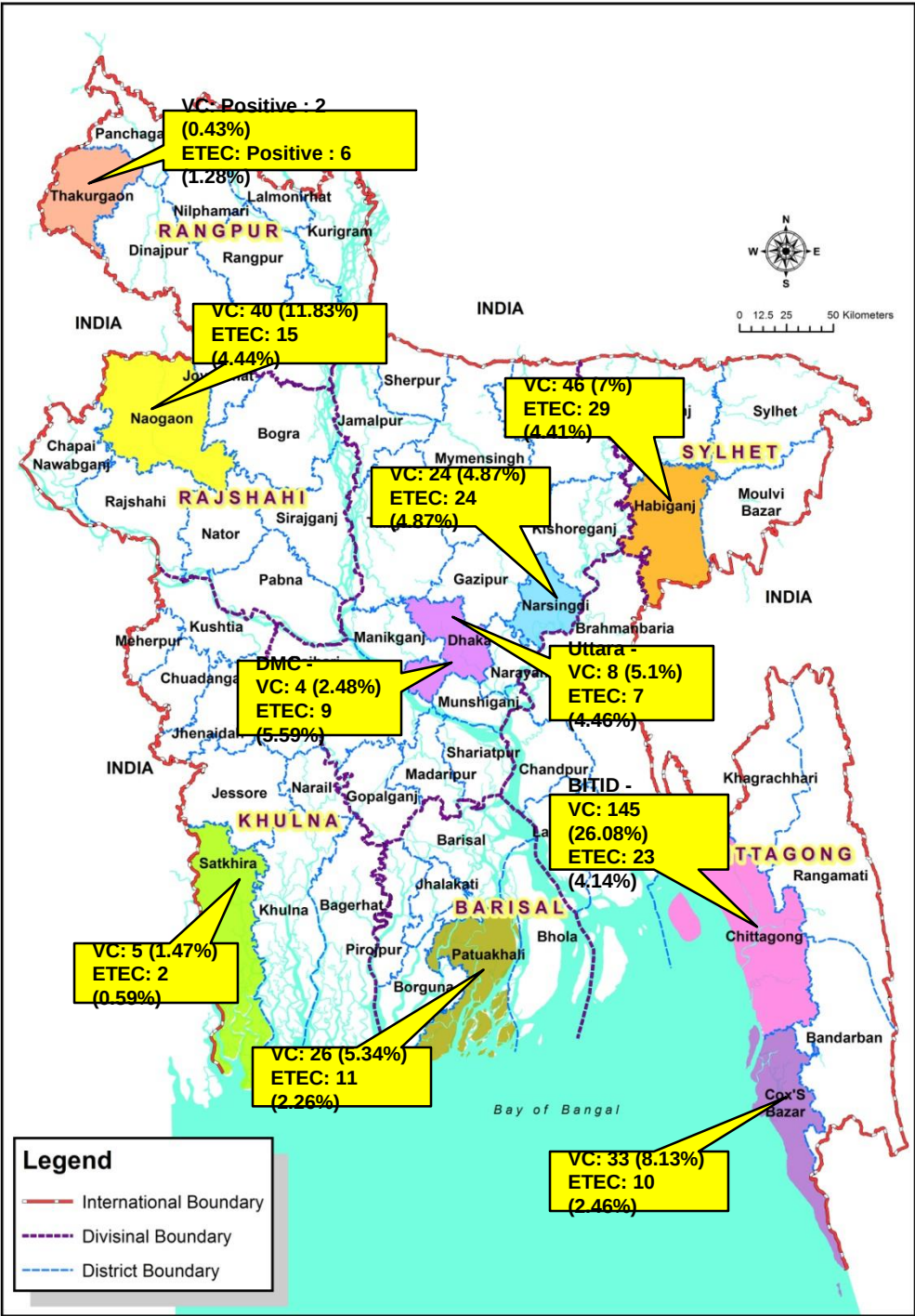
Distribution of ETEC cases in 2% surveillance system of the icddr,b Dhaka Hospital



March, 2016, 18% of ETEC in the 2% Surveillance system of the icddr,b hospital

Nationwide surveillance on ETEC in Bangladesh carried out in the Upazilla hospitals and other health facilities

Study in 7 divisions of Bangladesh 10 sites (2013-2015; ongoing)



Towards better understanding ETEC infections and protective mechanisms for vaccine evaluation

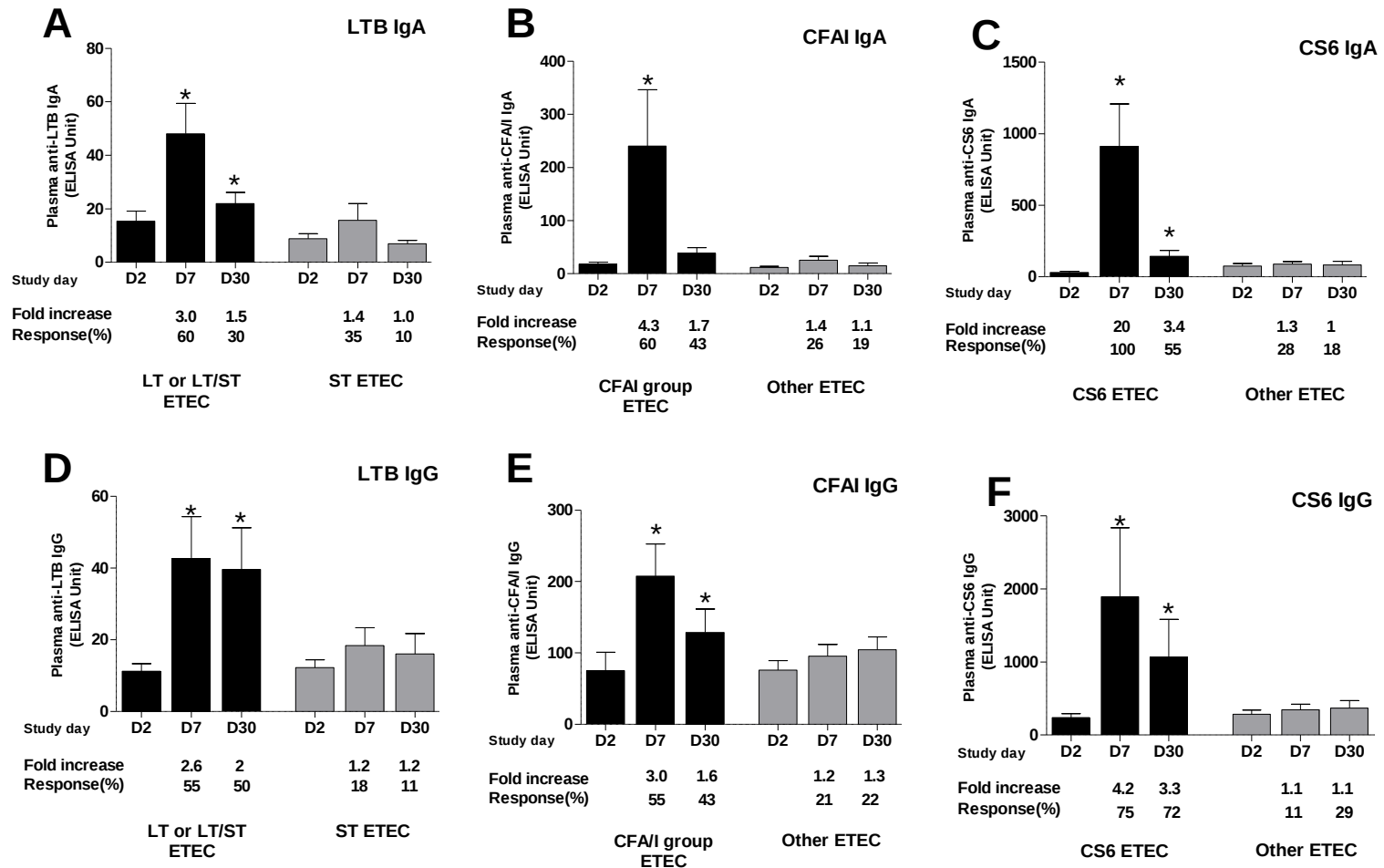
ETEC diarrheal infections trigger mucosal immune responses which are not easy to study using invasive procedures such as small intestinal biopsies

Surrogate markers of local responses can be studied in secretions and in blood to decipher the nature of the B and T cell response

The potential destination of circulating antigen specific antibody secreting cells can be investigated by studying the expression of gut homing markers

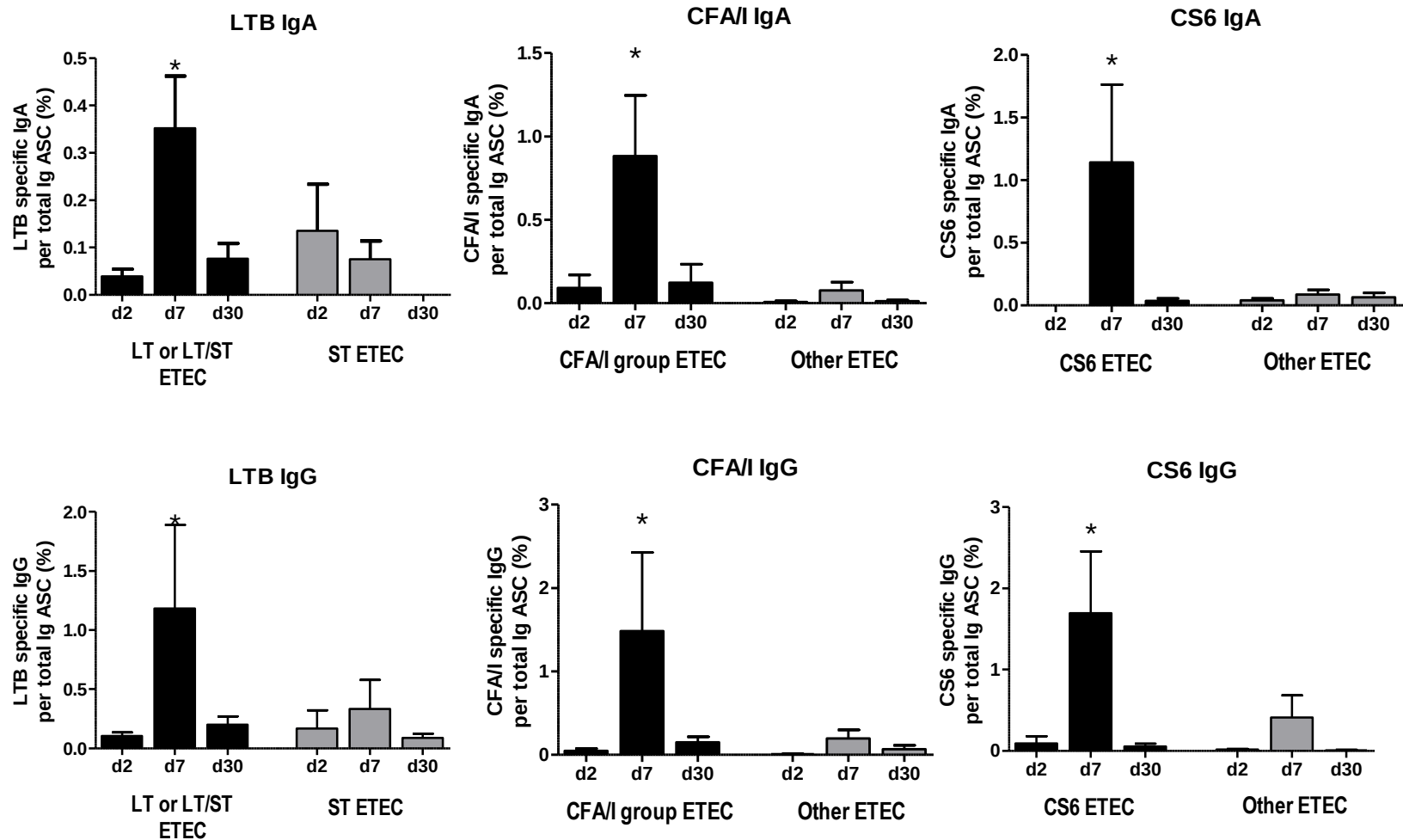
A more targeted immune response can be associated with longer lasting immunity

LTB, CFA/I and CS6 specific antibody responses in plasma of Bangladeshi adults with ETEC diarrhea



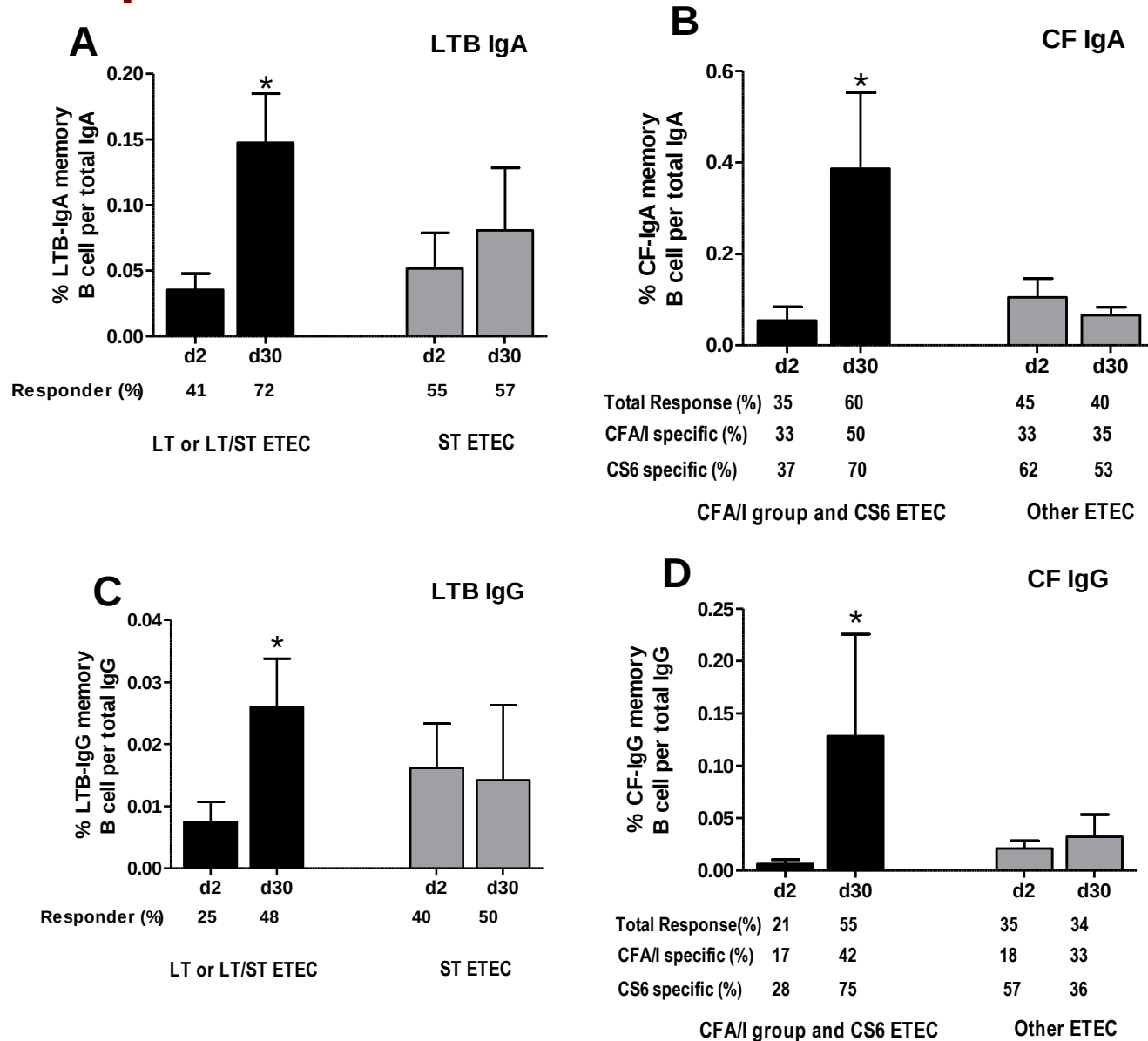
Increased levels of plasma IgA and IgG antibodies at day 7 after onset ETEC diarrhea to different antigens

Circulating ASC responses to LTb, CFA/I and CS6 in adult Bangladeshi ETEC patients

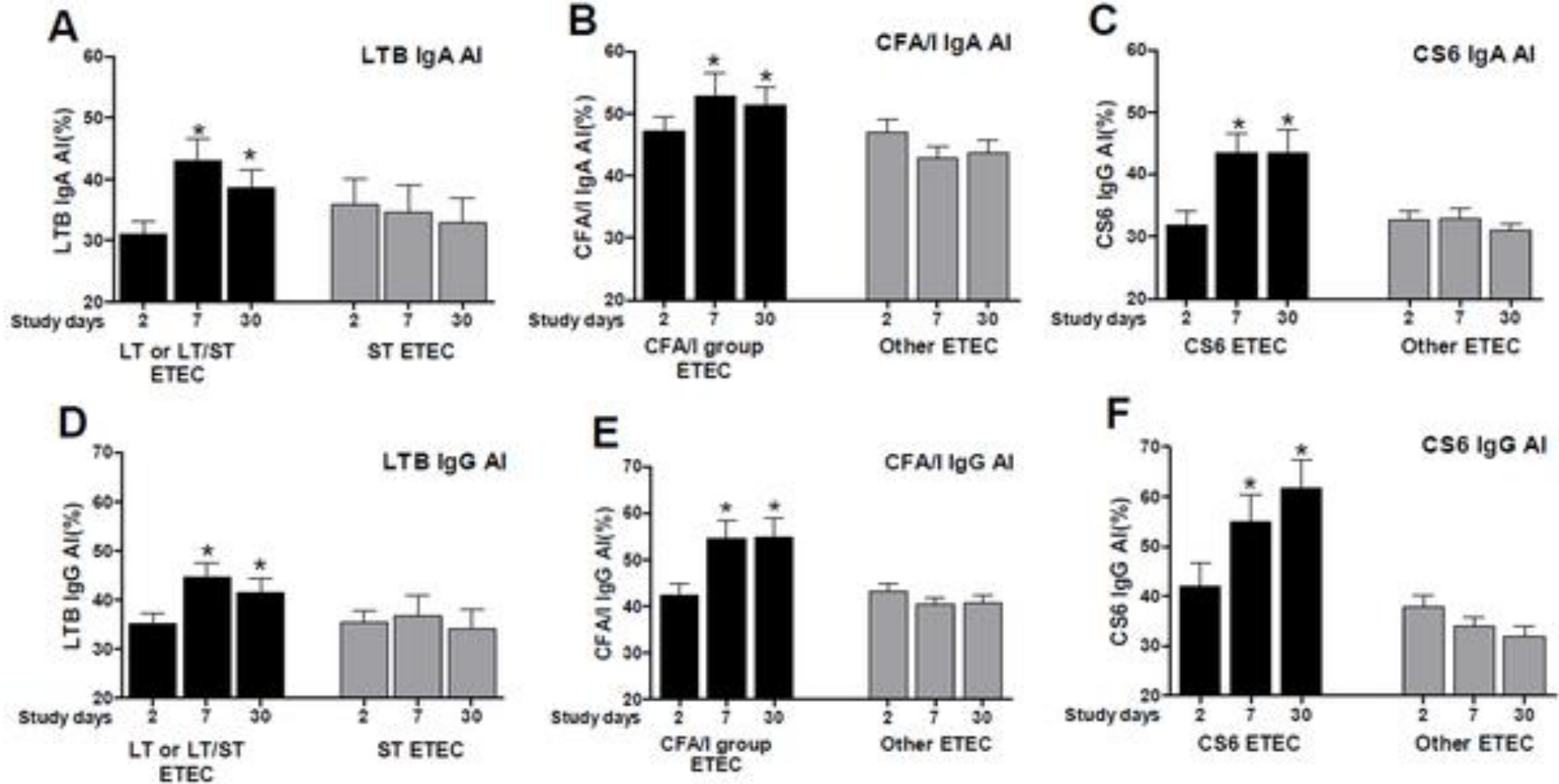


Increased circulating ASCs of IgA and IgG isotypes at day 7 after onset of ETEC diarrhea

LTB and CF specific memory B cell responses in patients infected with ETEC diarrhea

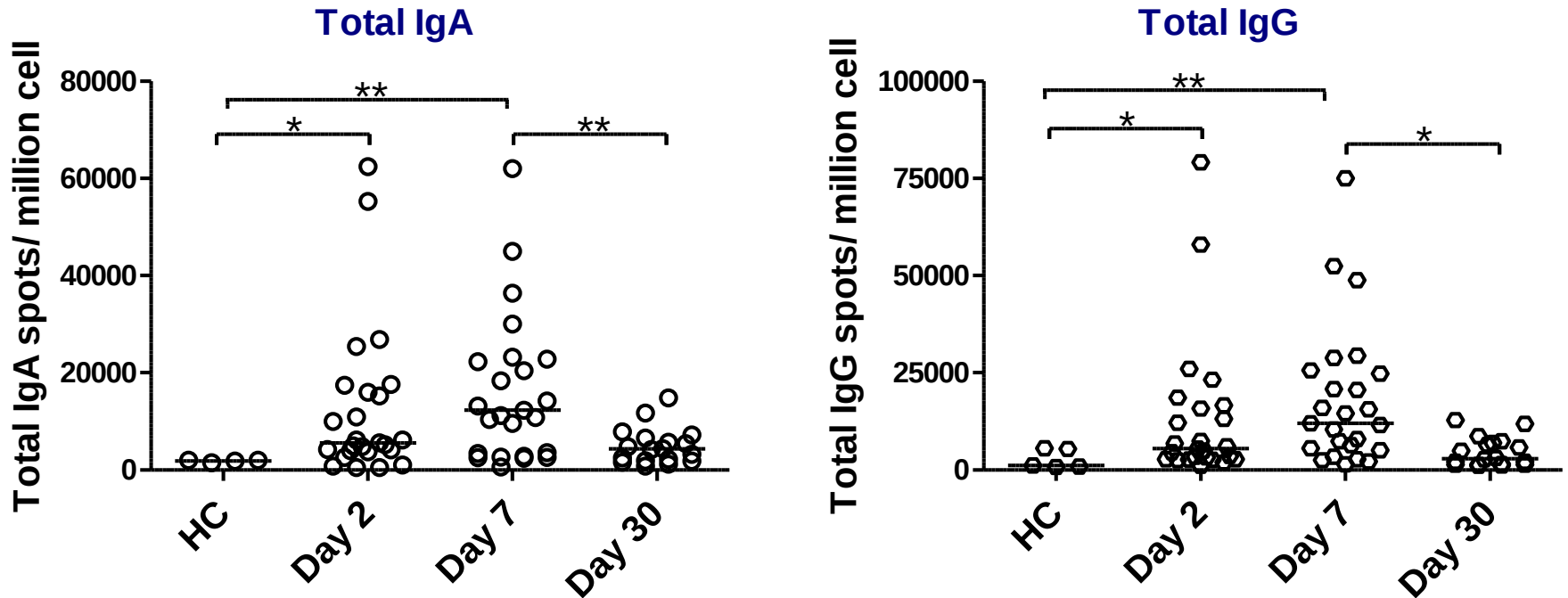


Avidity indices of LTB (A and D), CFA/I (B and E) and CS6 (C and F) specific IgA and IgG antibodies in plasma in Bangladeshi adults infected with ETEC



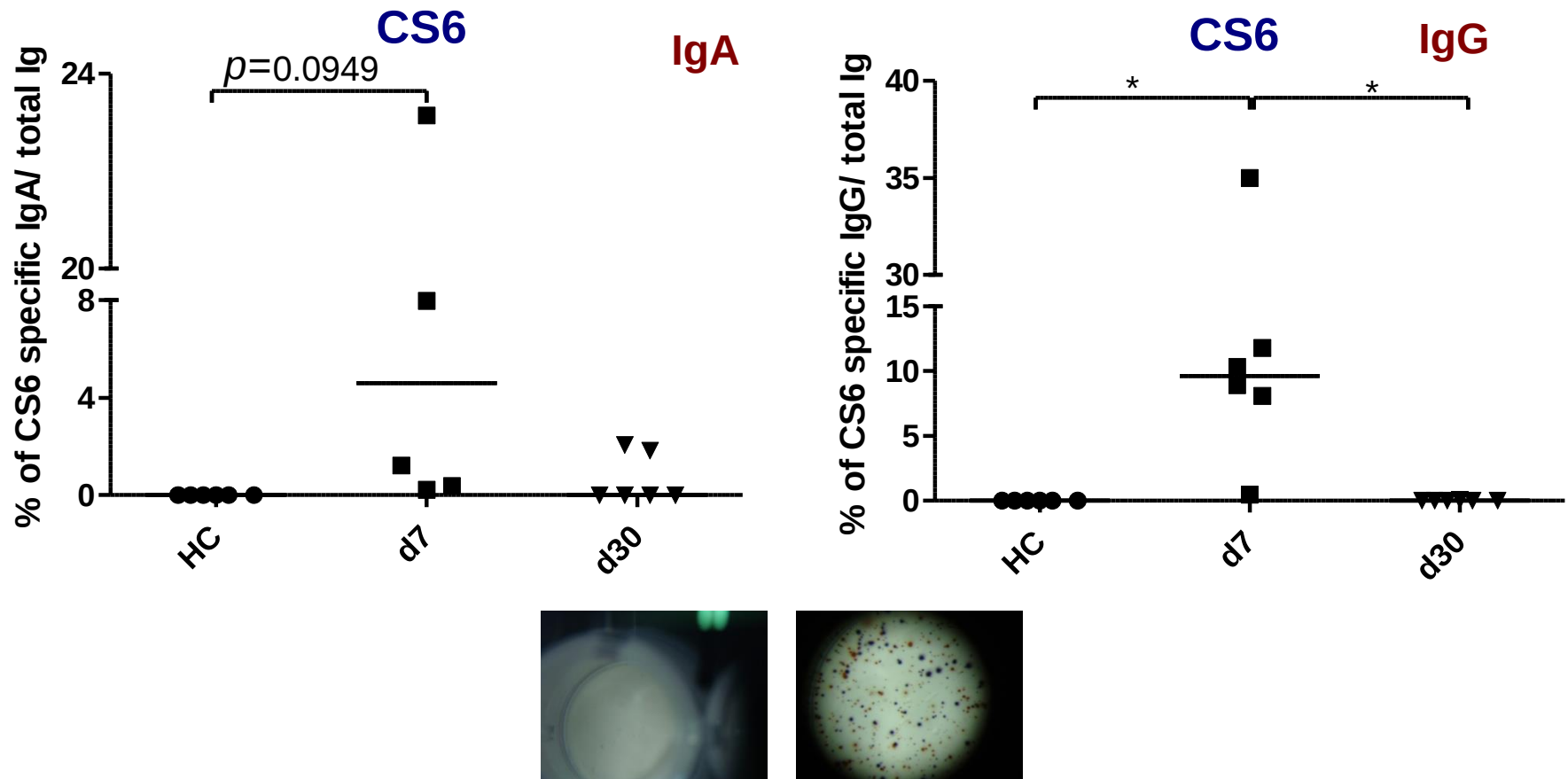
↑ Avidity indices at day 7 remained elevated up to day 30 in patients infected with ETEC expressing LT or LT/ST, CFA/I and CS6

Total gut-homing ($\beta 7^+$) ASC responses in ETEC patients



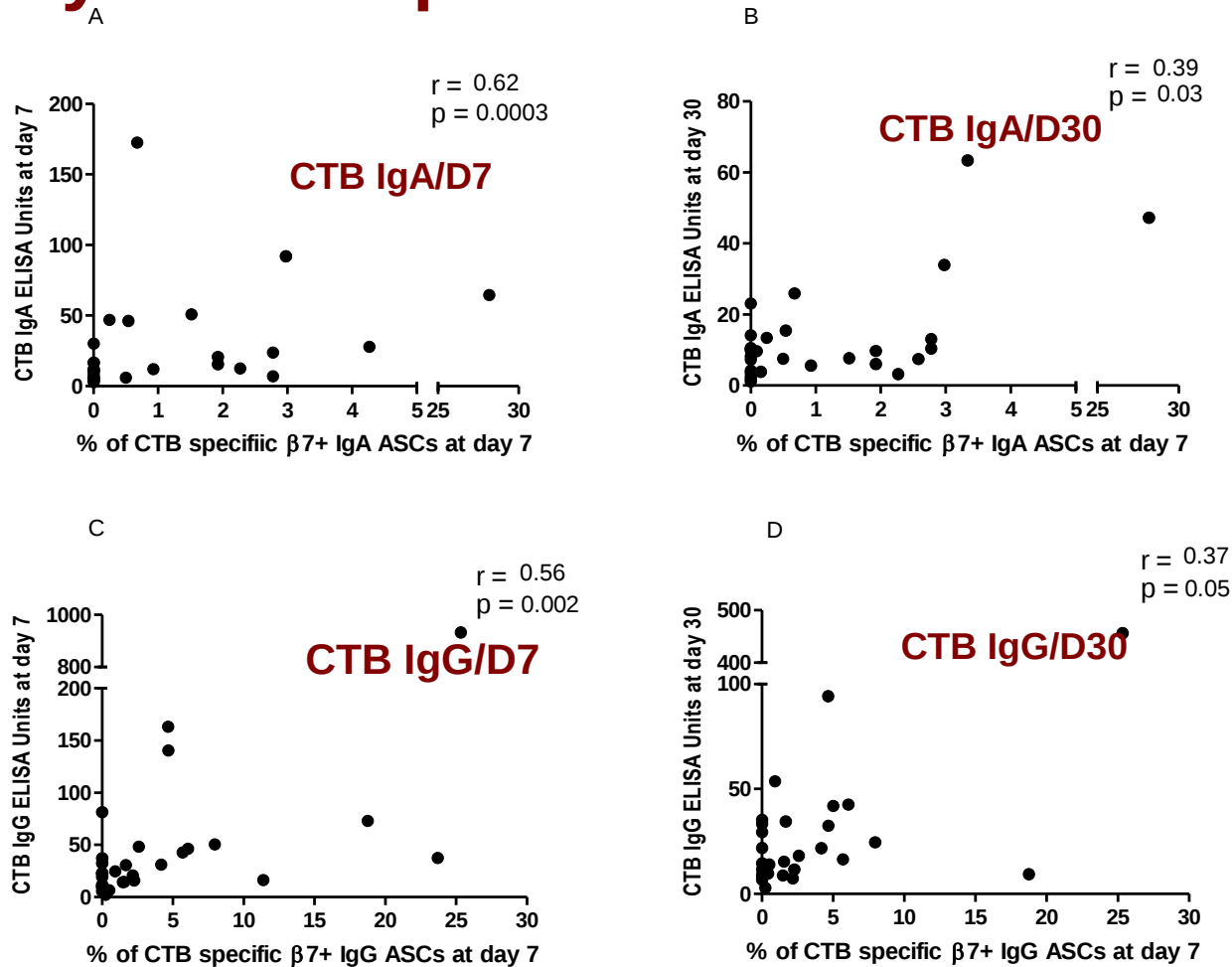
Increased levels of gut homing total immunoglobulin (IgA and IgG) were observed at day 7 after onset of ETEC diarrhea

CS6 specific gut homing ($\beta 7^+$) ASC responses in ETEC patients



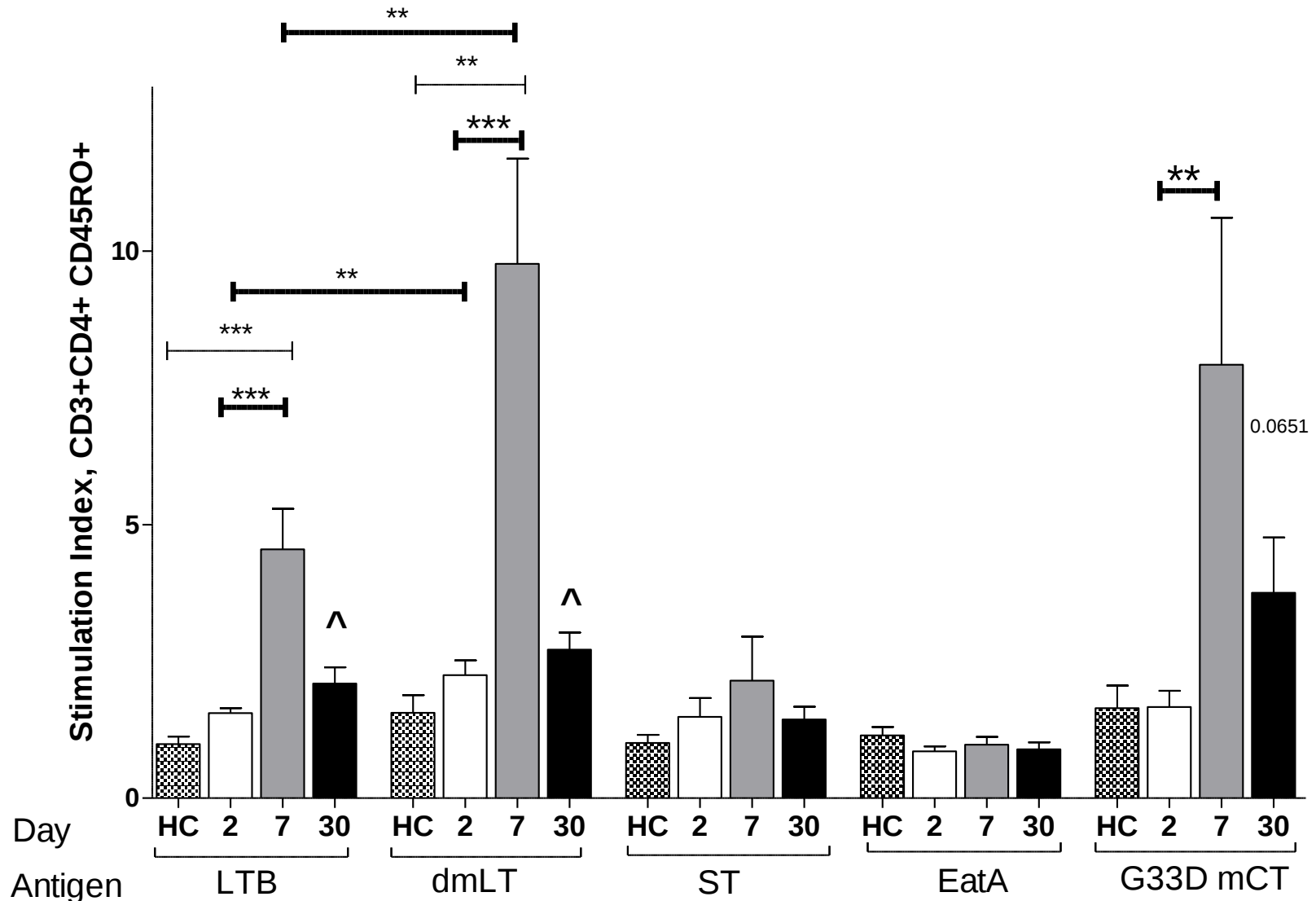
↑ CS6 specific IgA and IgG responses were observed at day 7

Association of gut-homing ASCs with plasma antibody titers in patients with ETEC infection



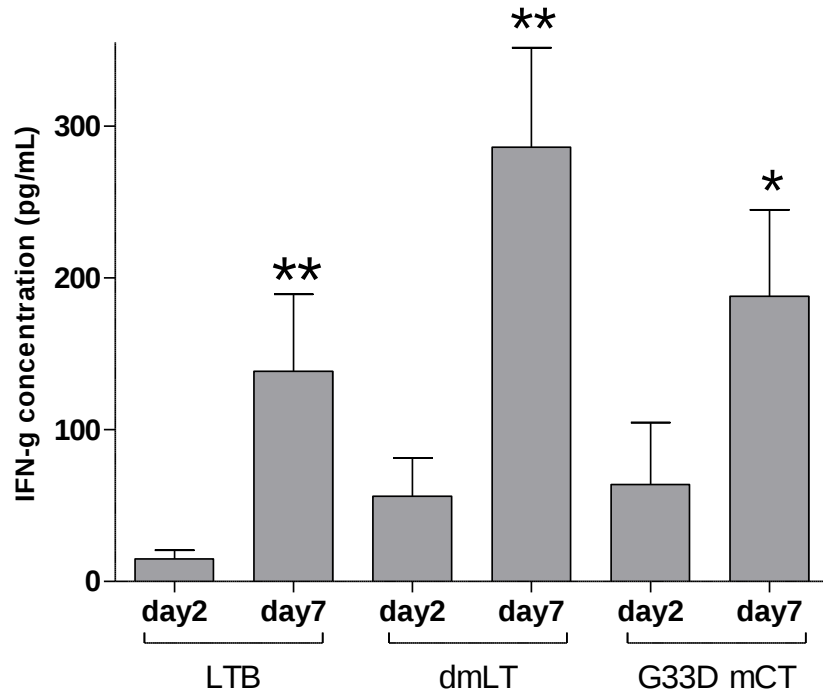
ETEC specific gut-homing IgA and IgG ASCs at day 7 were positively correlated with specific IgA and IgG antibodies on days 7 and 30 post onset of diarrhea

Antigen specific Memory helper T cell responses

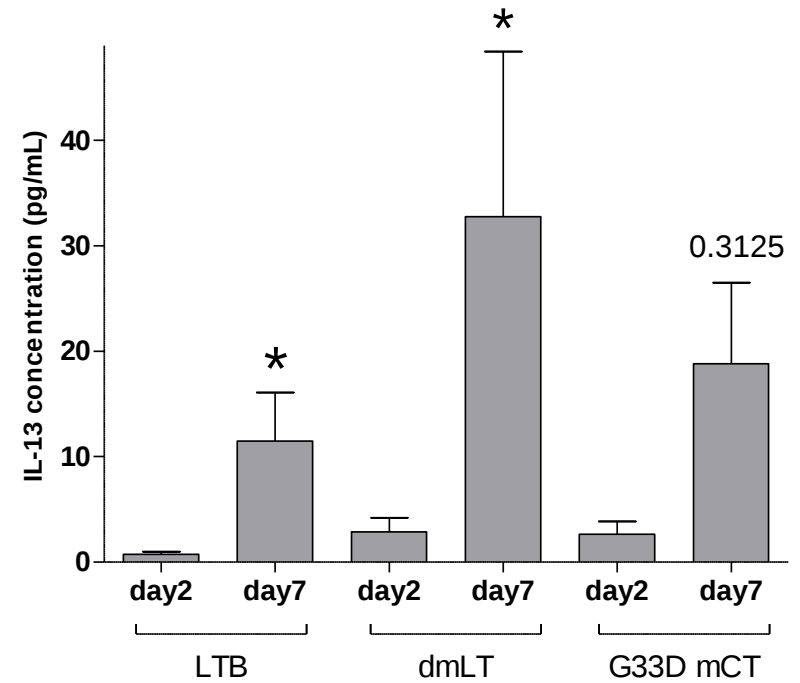


Cytokine responses

IFN- γ ELISA



IL-13 ELISA



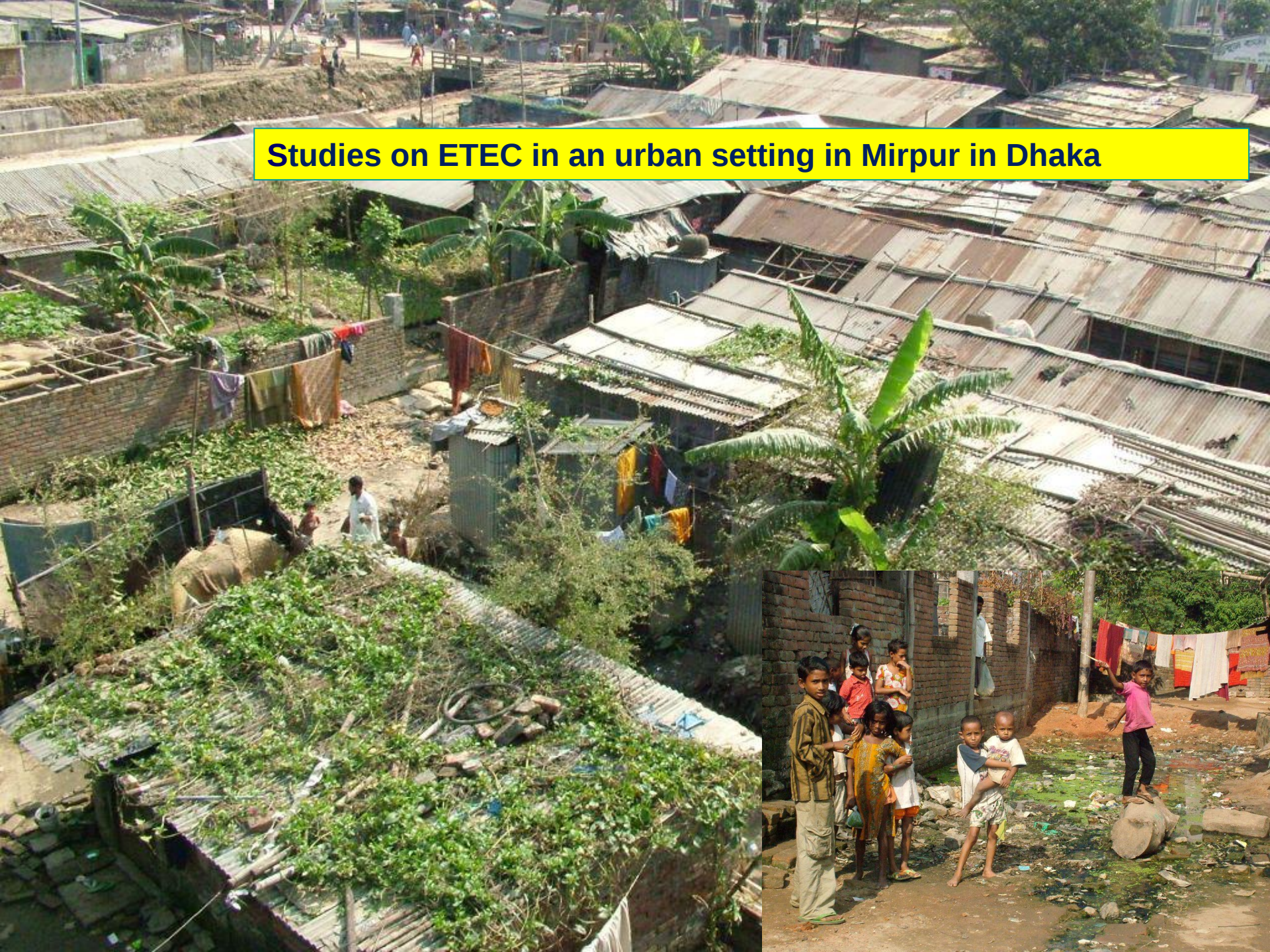
Birth cohort study on ETEC and relatedness of ETEC diarrhea with blood group antigen

Studies on children in a birth cohort in Mirpur have shown :

- ETEC infections cause stunting in children.
- Children with CFA/I ETEC diarrhea are protected from homologous ETEC infection
- Children with histoblood group AB and A have increased susceptibility to ETEC infection
- Children with Lewis blood group Le(a+b-) are more susceptible to CFA/I diarrhea
- Lewis blood group 'a' antigen may be a candidate receptor for ETEC colonization factor CFA/I

CFA/I (LT:ST:LT/ST = 0:36:5)	Symptomatic	7 (17)	6 (6)	0.075
	Asymptomatic	9 (22)	19 (19)	NS
CFA/I group fimbriae (CFA/I, CS14, and CS17) (LT:ST:LT/ST = 8:55:10)	Symptomatic	11 (27)	11 (11)	0.032
	Asymptomatic	13 (32)	38 (37)	NS
CFA/I group including strains co-expressing CS3 (CFA/I, CS14, CS17, CS1+CS3, and CS2+CS3) (LT:ST:LT/ST = 10:69:18)	Symptomatic	18 (44)	16 (16)	<0.001
	Asymptomatic	16 (40)	47 (46)	NS
CFA/II group (CS3 only, CS1+CS3, and CS2+CS3) (LT:ST:LT/ST = 2:15:12)	Symptomatic	10 (24)	5 (5)	0.002
	Asymptomatic	5 (12)	9 (9)	NS
CS6 (CS6 only and CS5+CS6 strains) (LT:ST:LT/ST = 3:38:18)	Symptomatic	8 (20)	17 (17)	NS
	Asymptomatic	9 (22)	25 (25)	NS

Studies on ETEC in an urban setting in Mirpur in Dhaka



Conclusions

- ETEC induces memory B cells and high avidity antibodies to LTB and CFs that could mediate anamnestic responses on re-exposure to ETEC and may help in understanding the requirements for designing and following effectiveness of vaccines
- Need to evaluate whether memory responses, affinity maturation and level of antibodies to these ETEC antigen correlate with protection following vaccination
- Vaccine studies can now include studies of mucosal gut homing ASC in young children and infants using low volumes of blood using the cell sorting and ELISPOT technique
- Measurement of ALS/ASC and plasma antibody levels within 5 days of second/booster dose of oral vaccines is critical for gauging the peak of the responses in endemic settings
- Relationship of ABO and Lewis blood group and genetic factors on response to oral vaccines is an area that needs to be given attention
- ETVAX vaccine is now in the infant phase with encouraging results of safety in all age groups