Gastroenteritis remains a leading cause of morbidity and mortality worldwide and is the second commonest cause of death in young children in resource poor settings, responsible for an estimated 578, 000 deaths in children under the age of five in 2013[[1](#_ENREF_1)]. The introduction of rotavirus vaccines in > 60 countries globally between 2006 and 2013 has contributed to significant reductions in the burden of rotavirus diarrhoea, and the number of deaths in children <5 halved between 2000 and 2013 ( form an estimated 528,000 to 215, 000)[[2](#_ENREF_2)]. Despite their impact, rotavirus vaccines are significantly less effective in children living in resource poor countries in Asia and Africa [[3](#_ENREF_3),[4](#_ENREF_4)], where the majority of rotavirus deaths occur. Whilst live attenuated vaccines such as OPV have had great success in eliminating the circulation of poliovirus from most countries, there is ample evidence showing that oral vaccines against poliomyelitis, cholera and shigellosis are less immunogenic among children living in low income countries[[5](#_ENREF_5)], and their effectiveness is compromised in those populations who need them most. The reasons for the poorer responses to rotavirus vaccines in low income countries are not fully understood but in addition to the potential strain heerogeneity on differential efficacy [[6](#_ENREF_6)], various host factors such as maternal antibody, age at vaccination, endemicity of infections such as Malaria, TB or HIV, persistent exposure to enteric pathogens in the environment, altered gut microbiota and malnutrition and micronutrient deficiencies all of which are intimately interlinked and believed to impact significantly in the underperformance of rotavirus vaccines.

I this issue, Harris *et al* explore differences in faecal microbiota composition between Ghanaian infants who seroconverted after rotavirus vaccination and those who did not, and compared them to the microbiota in unvaccinated Dutch children of matched age. They found significant differences in the overall microbiota composition between respondents and non-respondents, and they also observed that the microbiota of respondent Ghanaian infants was more similar to that of Dutch infants that to the non-respondent Ghanaian infants, establishing a correlation between rotavirus vaccine immunogenicity and faecal microbiota composition.

The human microbiota, particularly in the intestinal tract has been an area of intense research in recent years as its role in controlling metabolic and physiological functions from nutrient utilisation and the synthesis of vitamins to intestinal and immunological development and maturation is becoming increasingly understood[[7-11](#_ENREF_7)]. The role of the intestinal microbiota on the correct development and maturation of the immune system has been extensively studied in germ free animal models, providing insights into the mechanisms by which the microbiota shapes immune maturation and responses[[12](#_ENREF_12),[13](#_ENREF_13)]. But infections can also lead to microbiome perturbations such as loss of diversity and outgrowth of opportunistic bacteria, and adaptive immune responses directed to commensal bacteria [[14](#_ENREF_14),[15](#_ENREF_15)]. Fruthermore, studies in Malawi and Bangladesh have recently found strong associations between the microbiome composition and malnutrition[[16](#_ENREF_16),[17](#_ENREF_17)].

To date, the relevance of the intestinal microbiota to oral vaccine efficacy remains under-investigated, but given the increasing evidence demonstrating the impact of the intestinal microbiota on the early development of immune function, it is reasonable to expect that it will also influence immune responses to vaccines. The role of the gut microbiota in promoting immunity to influenza vaccination has recently come to light [[18](#_ENREF_18)]. Toll-like receptor 5 (TLR5)-mediated pathway is critical for non-replicating influenza vaccine efficacy and it is dependent on the gut microbiota to provide the stimuli for development of plasma cells and antibody production. This pathway may however not be applicable to live or adjuvanted vaccines. Bacterial lippolysacharide (LPS) is a potent stimulant of the innate immune system, however, differences in the LPS composition among bacterial species differ significantly in their immune stimulatory properties[[19](#_ENREF_19)]. Harris et al speculate that the positive association between bacteria related to *Streptococcus bovis* and seroconversion in Ghanaian infants may relate to their potential to be opportunistic pathogens triggering inflammatory responses, and hence act as adjuvants. On the other hand, bacteria of the phylum Bacteroidetes were more abundant in the non-responders, and the potential that this observation may correlate with colonisation with bacteria possessing LPS inhibits innate immune signalling and endotoxin tolerance warrants further research.

 But similarly to commensal bacteria the virome can support intestinal homeostasis and shape mucosal immunity [[20](#_ENREF_20)] and eukaryotic components of the microbiome have also been reported to impact on chronic inflammatory disorders [[21](#_ENREF_21)]. However, the virome and the prokaryote microbiome are currently far less well studied.

Inflammation and degree of immune system activation also have a significant impact on vaccine efficacy. In a recent yellow fever vaccine trial in healthy Swiss and Ugandan volunteers, the pre-existing activation level of CD8 + T-cells and B-cells as well as pro-inflammatory monocytes at the time of vaccination correlated with reduced responses in the Ugandan volunteers[[22](#_ENREF_22)]. A negative association between enteric virus infections and reposes to polio and rotaviorus vaccines has also recently been recognised in separate studies, with enterovirus infections correlating with poor responses to both rotavirus and oral polio vaccines [[23](#_ENREF_23),[24](#_ENREF_24)]. Enteric live-attenuated vaccines need to replicate in the intestinal tract, in direct interaction with the intestinal flora, hence the microbiota is also likely to directly and/or indirectly impact on efficient vaccine strain replication, necessary to elicit a protective local immune response. The microbiota has been shown to influence enteric virus replication both in vitro and in vivo, using two different strategies; either by facilitating virus entry and infections, or by altering antiviral immune responses in a way that promotes viral infections[[25](#_ENREF_25),[26](#_ENREF_26)]

A recent study in Ecuador has also identified that infections with helminths in pregnancy correlated with significant increases in immune responses to polio and rotavirus vaccines in the infants, stretching further the potential impact of the microbiome on immune responses to vaccines to include maternal microbiome and eukaryotic infections[[27](#_ENREF_27)] .

Therefore, acute and persistent infections with diverse pathogens and the microbiome composition interact in maintaining immune homeostasis and gut health, with an expected direct effect on vaccine take, immunogenicity and efficacy.

Understanding the role of the microbiota in vaccine response, in inherently different populations, will allow the design of specific interventions that favour the colonisation of the infant gut with those bacteria that promote vaccine replication and strong immune responses. The use of probiotics for treating RV disease has been shown to be beneficial by shortening the duration and decreasing the severity of diarrhoea31. Probiotic supplementation before and during RV vaccination increases RV vaccine immunogenicity (in co-administration with zinc; Kang *et al*, under review).

1. Liu L, Oza S, Hogan D, Perin J, Rudan I, et al. (2015) Global, regional, and national causes of child mortality in 2000-13, with projections to inform post-2015 priorities: an updated systematic analysis. Lancet 385: 430-440.

2. Tate JE, Burton AH, Boschi-Pinto C, Parashar UD (2016) Global, Regional, and National Estimates of Rotavirus Mortality in Children <5 Years of Age, 2000-2013. Clin Infect Dis 62 Suppl 2: S96-S105.

3. Bar-Zeev N, Jere KC, Bennett A, Pollock L, Tate JE, et al. (2016) Population Impact and Effectiveness of Monovalent Rotavirus Vaccination in Urban Malawian Children 3 Years After Vaccine Introduction: Ecological and Case-Control Analyses. Clin Infect Dis 62 Suppl 2: S213-219.

4. Bhandari N, Rongsen-Chandola T, Bavdekar A, John J, Antony K, et al. (2014) Efficacy of a monovalent human-bovine (116E) rotavirus vaccine in Indian infants: a randomised, double-blind, placebo-controlled trial. Lancet 383: 2136-2143.

5. Pasetti MF, Simon JK, Sztein MB, Levine MM (2011) Immunology of gut mucosal vaccines. Immunol Rev 239: 125-148.

6. Velasquez DE, Parashar UD, Jiang B (2014) Strain diversity plays no major role in the varying efficacy of rotavirus vaccines: an overview. Infect Genet Evol 28: 561-571.

7. Leblanc JG, Milani C, de Giori GS, Sesma F, van Sinderen D, et al. (2012) Bacteria as vitamin suppliers to their host: a gut microbiota perspective. Curr Opin Biotechnol.

8. Sonnenburg JL, Backhed F (2016) Diet-microbiota interactions as moderators of human metabolism. Nature 535: 56-64.

9. Yamada T, Takahashi D, Hase K (2016) The diet-microbiota-metabolite axis regulates the host physiology. J Biochem 160: 1-10.

10. Slack E, Hapfelmeier S, Stecher B, Velykoredko Y, Stoel M, et al. (2009) Innate and adaptive immunity cooperate flexibly to maintain host-microbiota mutualism. Science 325: 617-620.

11. Atarashi K, Honda K (2011) Microbiota in autoimmunity and tolerance. Curr Opin Immunol 23: 761-768.

12. Hooper LV, Littman DR, Macpherson AJ (2012) Interactions between the microbiota and the immune system. Science 336: 1268-1273.

13. Hand TW (2016) The Role of the Microbiota in Shaping Infectious Immunity. Trends Immunol 37: 647-658.

14. Brown EM, Wlodarska M, Willing BP, Vonaesch P, Han J, et al. (2015) Diet and specific microbial exposure trigger features of environmental enteropathy in a novel murine model. Nat Commun 6: 7806.

15. Hand TW, Dos Santos LM, Bouladoux N, Molloy MJ, Pagan AJ, et al. (2012) Acute gastrointestinal infection induces long-lived microbiota-specific T cell responses. Science 337: 1553-1556.

16. Smith MI, Yatsunenko T, Manary MJ, Trehan I, Mkakosya R, et al. (2013) Gut microbiomes of Malawian twin pairs discordant for kwashiorkor. Science 339: 548-554.

17. Subramanian S, Huq S, Yatsunenko T, Haque R, Mahfuz M, et al. (2014) Persistent gut microbiota immaturity in malnourished Bangladeshi children. Nature 510: 417-421.

18. Oh JZ, Ravindran R, Chassaing B, Carvalho FA, Maddur MS, et al. (2014) TLR5-Mediated Sensing of Gut Microbiota Is Necessary for Antibody Responses to Seasonal Influenza Vaccination. Immunity 41: 478-492.

19. Vatanen T, Kostic AD, d'Hennezel E, Siljander H, Franzosa EA, et al. (2016) Variation in Microbiome LPS Immunogenicity Contributes to Autoimmunity in Humans. Cell 165: 842-853.

20. Kernbauer E, Ding Y, Cadwell K (2014) An enteric virus can replace the beneficial function of commensal bacteria. Nature 516: 94-U223.

21. Li QR, Wang CY, Tang C, Ms QH, Li N, et al. (2014) Dysbiosis of Gut Fungal Microbiota is Associated With Mucosal Inflammation in Crohn's Disease. J Clin Gastroenterol 48: 513-523.

22. Muyanja E, Ssemaganda A, Ngauv P, Cubas R, Perrin H, et al. (2014) Immune activation alters cellular and humoral responses to yellow fever 17D vaccine (vol 124, pg 3147, 2014). Journal of Clinical Investigation 124: 4669-4669.

23. Grassly NC, Praharaj I, Babji S, Kaliappan SP, Giri S, et al. (2016) The effect of azithromycin on the immunogenicity of oral poliovirus vaccine: a double-blind randomised placebo-controlled trial in seronegative Indian infants. Lancet Infect Dis 16: 905-914.

24. Taniuchi M, Platts-Mills JA, Begum S, Uddin MJ, Sobuz SU, et al. (2016) Impact of enterovirus and other enteric pathogens on oral polio and rotavirus vaccine performance in Bangladeshi infants. Vaccine 34: 3068-3075.

25. Kuss SK, Best GT, Etheredge CA, Pruijssers AJ, Frierson JM, et al. (2011) Intestinal microbiota promote enteric virus replication and systemic pathogenesis. Science 334: 249-252.

26. Karst SM (2016) The influence of commensal bacteria on infection with enteric viruses. Nature Reviews Microbiology 14: 197-204.

27. Clark CE, Fay MP, Chico ME, Sandoval CA, Vaca MG, et al. (2016) Maternal Helminth Infection Is Associated With Higher Infant Immunoglobulin A Titers to Antigen in Orally Administered Vaccines. Journal of Infectious Diseases 213: 1996-2004.

 Enteric vaccines must provide a strong local immune response; hence, development efforts have been focused mostly on oral live attenuated vaccines. In resource poor countries, live oral vaccines provide additional benefits both in terms of ease of administration but also indirect effects such as secondary spread to immunised contacts (eg OPV).

While the extent of interaction can be expected to go substantially

beyond current knowledge, analysis

. Similarly, the importance of intestinal fl ora

composition has been demonstrated for TLR7-stimulated development

of infl ammasomes in respiratory mucosa, where lack of

TLR7 ligands leads to impaired immune response s to infl uenza

[ 53 , 54 ]. Likewise, it has recently been shown that pathogen -free

mice are more sensitive to infl uenza challenge than other mice and

that infl ammation can be dampened via colonization with

*Streptococcus aureus* in a TLR2-dependent way [ 55 ]. However,

respiratory infl uenza infection can lead to gastroenteritis-like

symptoms not via direct infection of gut epithelia, but rather due

to a shift in gut microbiota leading to increase in Th17 cells in the

small intestine and also enhanced IL15/IL17A production, an

effect abolished by antibiotics [ 56 ]. Possibly adding some detail to

this observation, Weber et al. conclude that IL17-producing thymocytes

form a “fi rst line of recognition” stimulated by cell wall

components of diverse pathogenic and apathogenic bacteria, but

that effector molecules such as IL-6 and IFN-γ determine transition

to a pathological infl ammation [ 57 ]. It has also been demonstrated

that microbiota depletion impairs early innate immunity

against the pathogen *Klebsiella pneumoniae* and that this state can

be remedied by providing NOD-like (NLR) receptor ligands but

not Toll- like receptor (TLR) ligands from the gastrointestinal

tract, whereas NLR ligands from the upper respiratory tract were

ineffective [ 58 ]. This highlights the systemic impact of local microbiota

on immune responses and suggests a critical importance of

microbiota derived pattern recognition receptor (PRR) ligands for

establishing effective immunity. In summary it can be stated that

current evidence shows heavy dependency of microbiota and

microbiota composition on activity of the immune system and effi cacy

of at least some of the vaccines. Bacteria are not the only microorganisms

modulating the immune system; the virome can support

intestinal homeostasis comparable to bacterial commensals, presumably

by providing equivalent stimuli [ 59 , 60 ]. Similarly, fungal

diversity and species composition may prove to be a critical extension

also in other areas than chronic infl ammatory disorders of the

gut [ 61 ]. The terrible and disfi guring childhood disease Noma

(cancrum oris) is currently thought to be caused by malnutrition

and microfl ora dysbiosis [ 62 ]. There is also clear evidence that the

choice of food impacts microbiome development and ultimately

immune competence [ 63 ]. The interplay of human nutrition, gut

microbiome, immune system development and competence, dysfunction,

and vaccine effi cacy is the focus of ongoing research and

is now viewed as a very likely critical dimension of immunology

and hence possibly also vaccinology [ 63 – 69 ]. The impact of microbiota

and microbial diversity on vaccine effi cacy in infants has

recently been investigated in a small cohort by Huda et al. where

they suggest probiotics for minimizing dysbiosis [ 70 ]. Of note in

this context, while microbiota have emerged as an important

immunological dimension, metagenomics has emerged as a powerful

tool for analysis of the microbial community in an organism.

Metagenomics could be used to identify and quantitate the gut

microbiota of the fecal samples. Several other body (especially

mucosal) surfaces are commonly covered by microbial communities;

within the gastrointestinal system several distinct regions exist

which contain microbiota of typically different composition.

Moreover, the gel layer and luminal communities of gut microbiota

have been shown to feature different population composition

[ 71 ]. Finding ways to routinely access these spatial dimensions in

health and disease may open yet another possible critical aspect for

integration into the growing number of systems components

regarding immunity and also vaccine effects. The gut glycome is

another uninvestigated area presumably providing substantial

immunologically relevant mass to the human body.

The distinction between a commensal and a pathogen can be

diffi cult to draw, depending on the potential to be involved in disease.

Examples of organism with potential impact on vaccinology

are immune-distorting bacteria like Mycoplasma species which can

cause diverse diseases in animals and humans [ 72 ] but are also nonobvious

(and often unidentifi ed) microbes of the natural microbiome

[ 72 , 73 ]. As multiple roles have been suggested for the human

pathogen *M. pneumoniae* this may either mean a substantial underappreciation

of other causes of atypical pneumonia or otherwise of

other factors contributing to the conversion from an asymptomatic

infection to a severe disease. Mycoplasma species are also frequently

associated with autoimmune diseases [ 74 ]. The mechanism by

which Mycoplasmas modulate the immune system are not clear,

and part of the reason is that these pathogens may contribute to a

pro-infl ammatory or otherwise immunologically biased environment

rather than being clear-cut pathogens in the sense of Koch’s

postulates. At least in chicken severe exacerbation of otherwise

asymptomatic (avian) infl uenza infection with *M. gallisepticum* , a

Mycoplasma phylogenetically close to *M. pneumoniae* , has been

documented [ 75 ]. Several known interactions exist where these can

lead to nonadditive exacerbation of other infections through intensifi

ed infl ammatory responses. At least in Ureaplasma species the term

pseudospecies has been used, as different isolates may vary greatly in

their content of pathogenicity factors. In fact, from both a general

health and a vaccine perspective it may be equally critical to consider

the immuno-modulatory pathogenicity mechanisms available within

a person’s microbiome along with specifi c bacterial species, as their

combined effect may be very distinct or at least nonadditively amplifi

ed from individual factor contributions [ 76 ].

Another example of frequently observed chronic pathogen

includes the highly prevalent immune distorting viruses of genus

lymphocryptovirus comprising *Epstein* - *Barr virus* ( *EBV* ) and

*Cytomegalovirus* ( *CMV* ); these cause lifelong infections, and *EBV*

is known for its B-cell tropism. Both viruses can establish regulatory

complex periods of latency. The effect of *EBV* and *CMV* infection

versus age on immunity has recently been studied by Wang

et al. where they differentiated age-dependent and -independent

effects [ 77 ]. Specifi cally, decreased diversity of antibody repertoires

with accumulation of memory B-cells and lower naive B-cell populations

was associated with reduced vaccine effi cacy in the elderly.

They report that immune-globulin heavy chain (IGHV) mutation

frequency increases upon infection with *CMV* , but not *EBV. CMV*

infection tends to increase the proportion of highly mutated IgG

and IgM regions, but not IgA or IgD. The effect of *CMV* on

mutation rate is stronger with age, where the effect may stem from

the proportion of *CMV* -specifi c clones. Age and *EBV* infection

correlated with persistent clonal expansion, where very few clonal

lineages (possibly derived from a single ancestor) tend to be overrepresented.

In the study these expanded clones may be cases of

monoclonal B-cell lymphocytosis (MBL), a lymphoproliferative

disorder with some characteristics of CLL typically seen in the

elderly.

The infl ammatory status including degree of immune system

activation can have signifi cant impact on vaccine effi cacy. Recently

it was shown in a YF-17D (yellow fever vaccine) trial comparing

vaccination effi cacy of 50 volunteers in Lausanne (Switzerland)

versus the same number in Entebbe (Uganda) that the latter produced

less effective humoral and CD8 + responses. The authors

negatively correlated the pre-existing activation level of CD8 +

T-cells and B-cells as well as pro-infl ammatory monocytes at the

time of vaccination with this reduced response [ 78 ]. Admittedly it

would also be interesting to know the cause of this infl ammation,

as the specifi c reason may affect the impact on vaccines. On the

other hand the impact of pre-existing low-grade infl ammatory

conditions on vaccines is a recurring theme in the current review.

In this context it is evident that determining protectivity profi les

for vaccines is only one side of the coin. The other one is that the

status of the vaccine recipient regarding infl ammatory diseases,

nutrition, and pre-existing immunity needs to be considered to

understand inter-patient variability. Unfortunately the complex

interaction of multiple clinical and subclinical infections is poorly

understood. In the context of vaccines, infl ammation and potential

impact of chronically infecting pathogens and pathogen interactions

need to be addressed

53 Wu S, Jiang Z-Y, Sun Y-F et al (2013)

Microbiota regulates the TLR7 signaling

pathway against respiratory tract infl uenza A

virus infection. Curr Microbiol 67:414–422

54. Oh JZ, Ravindran R, Chassaing B et al (2014)

TLR5-mediated sensing of gut microbiota is

necessary for antibody responses to seasonal

infl uenza vaccination. Immunity 41:478–492

55. Wang J, Li F, Sun R et al (2013) Bacterial

colonization dampens infl uenza-mediated

acute lung injury via induction of M2 alveolar

macrophages. Nat Commun 4:2106

56. Wang J, Li F, Wei H et al (2014) Respiratory

infl uenza virus infection induces intestinal

immune injury via microbiota-mediated

Th17 cell-dependent infl ammation. J Exp

Med 211:2397–2410

57. Weber A, Zimmermann C, Kieseier BC et al

(2014) Bacteria and their cell wall components

uniformly co-activate interleukin- 17-

producing thymocytes. Clin Exp Immunol

178:504–515

58. Clarke TB (2014) Early innate immunity to

bacterial infection in the lung is regulated

systemically by the commensal microbiota via

nod-like receptor ligands. Infect Immun

82:4596–4606

59. Kernbauer E, Ding Y, Cadwell K (2014) An

enteric virus can replace the benefi cial function

of commensal bacteria. Nature 516:

94–98

Johannes Sollner

Cadwell K (2014) Expanding the role of the

virome: commensalism in the gut. J Virol

89:1951–1953

61. Li Q, Wang C, Tang C et al (2014) Dysbiosis

of gut fungal microbiota is associated with

mucosal infl ammation in Crohn’s disease.

J Clin Gastroenterol 48:513–523

62. Leila Srour M, Marck KW, Baratti-Mayer D

(2015) Noma: neglected, forgotten and a

human rights issue. Int Health 7:149–150

63. Tilg H, Moschen AR (2015) Food, immunity,

and the microbiome. Gastroenterology

148:1107–1119

64. Kamada N, Seo S-U, Chen GY, Núñez G

(2013) Role of the gut microbiota in immunity

and infl ammatory disease. Nat Rev

Immunol 13:321–335

65. Casanova J-L, Abel L (2013) The genetic

theory of infectious diseases: a brief history

and selected illustrations. Annu Rev Genomics

Hum Genet 14:215–243

66. Le Chatelier E, Nielsen T, Qin J et al (2013)

Richness of human gut microbiome correlates

with metabolic markers. Nature 500:541–546

67. Ferreira RBR, Antunes LCM, Finlay BB

(2010) Should the human microbiome be

considered when developing vaccines? PLoS

Pathog 6:e1001190

68. Kau AL, Ahern PP, Griffi n NW et al (2011)

Human nutrition, the gut microbiome and

the immune system. Nature 474:327–336

69. Valdez Y, Brown EM, Finlay BB (2014)

Infl uence of the microbiota on vaccine effectiveness.

Trends Immunol 35:526–537

70. Huda MN, Lewis Z, Kalanetra KM et al

(2014) Stool microbiota and vaccine responses

of infants. Pediatrics 134:e362–e372

71. Lavelle A, Lennon G, O’Sullivan O et al

(2015) Spatial variation of the colonic microbiota

in patients with ulcerative colitis and

control volunteers. Gut. doi: 10.1136/

gutjnl-2014-307873

72. Kurata S, Osaki T, Yonezawa H et al (2014)

Role IL-17A and IL-10 in the antigen

induced infl ammation model by Mycoplasma

pneumoniae. BMC Microbiol 14:156

73. Spuesens EBM, Fraaij PLA, Visser EG et al

(2013) Carriage of Mycoplasma pneumoniae

in the upper respiratory tract of symptomatic

and asymptomatic children: an observational

study. PLoS Med 10:e1001444

74. Ben Aissa-Fennira F, Sassi A, Bouguerra A,

Benammar-Elgaaied A (2011)

Immunoregulatory role for a public IgM

idiotype in the induction of autoimmune diseases

in Mycoplasma pneumoniae infection.

Immunol Lett 136:130–137

75. Stipkovits L, Egyed L, Palfi V et al (2012)

Effect of low-pathogenicity infl uenza virus

H3N8 infection on Mycoplasma gallisepticum

infection of chickens. Avian Pathol

41:51–57

76. Xiao L, Crabb DM, Dai Y et al (2014)

Suppression of antimicrobial peptide expression

by ureaplasma species. Infect Immun

82:1657–1665

77. Wang C, Liu Y, Xu LT et al (2014) Effects of

aging, cytomegalovirus infection, and EBV

infection on human B cell repertoires.

J Immunol 192:603–611

78. Muyanja E, Ssemaganda A, Ngauv P et al

(2014) Immune activation alters cellular and

humoral responses to yellow fever 17D vaccine.

J Clin Invest 124:3147–3158

79. Hotamisligil GS (2006) Infl ammation and