so far that methane was not released from hydrates during this Dansgaard–Oeschger event (and, by implication, probably not during earlier such events), and adds to a growing body of evidence that suggests hydrates did not respond appreciably to climate variations during the most recent glacial period[7].

The climate 12,000 years ago was globally about 2 °C cooler than today[8]. This, in turn, is as much as 5 °C cooler than that projected[9] for the year 2100. Scenarios in which little is done to reduce greenhouse-gas emissions will therefore take the climate system into a state that is much warmer than during any of the ice-age Dansgaard–Oeschger events[8,9]. So, although the transition studied by Petrenko *et al.* was the most-recent abrupt polar warming event in the geological record, it may not provide a particularly good analogue of future warming. Further modelling and isotopic constraints for today's system, and for other time periods (perhaps including the interglacial that preceded the most-recent ice age), are required to better understand the probability of future geological methane change[10].

The ^{14}C ratio reported by Petrenko *et al.* is also useful in itself, because it allows the authors to provide the first quantitative constraint on ^{14}C-free methane emissions (that is, those from geological sources) in the pre-industrial climate system — something that eluded workers from the same group in previous work[11], but which is possible today because estimates of ^{14}C production in ice can now be made more accurately. They estimate an upper limit of 15.4 teragrams of methane per year (Tg CH_4 yr^{-1}; 1 Tg is 10^{12} grams), which is much lower than the approximately 52 Tg CH_4 yr^{-1} estimated for the present day[1,2]. Natural geological methane emissions are expected to have been higher during the past than in modern times[12], and so the authors' estimate of emissions 12,000 years ago can be taken as an upper limit for today's climate system.

As the authors point out, if geological emissions today are indeed less than or equal to 15.4 Tg CH_4 yr^{-1}, rather than 52 Tg CH_4 yr^{-1}, then the difference of approximately 40 Tg CH_4 yr^{-1} needs to be accommodated by revising our estimates of anthropogenic ^{14}C-free emissions upward by about 25% — a substantial correction to our view of the contemporary methane cycle. Such a revision would imply that there is more scope to reduce human influence on climate than was thought, by reducing methane emissions associated with human activities.

Petrenko and colleagues' result comes at a crucial time for our understanding of atmospheric methane: unlike CO_2 levels, methane's concentration is rising at a rate close to that of high-end projections[13], and the total anthropogenic contribution has already been revised upward in more-recent estimates based on methane ^{13}C isotopic data[14]. Further work is needed to understand whether these studies can be reconciled with each other, and with other methane constraints obtained for Earth's past and present.

The new study provides a compelling example of how studying the past helps us to better understand the present Earth system. Atmospheric methane levels seem capable of surprising us at every turn, from the rapid increases examined by Petrenko *et al.* to a period of puzzling stability observed at the start of this century[15]. If nothing else, we should heed warnings from the past if we are to understand the potential role of methane in future climate change. ■

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GLOBAL HEALTH

Probiotic prevents infections in newborns

A major cause of death and disease in babies is the failure of their developing immune systems to block life-threatening infections. A clinical trial reports that the use of a probiotic can help to prevent such infections. SEE ARTICLE P.407

DANIEL J. TANCREDI

Infections continue to be a considerable cause of death and disease among infants in low- and middle-income countries[1]. Newborns are susceptible to infection because key parts of their immune systems are still developing and not fully functional, particularly in premature babies (born at less than 37 weeks of gestation) and those with a low birth weight[2,3]. Also of concern is a response to infection that results in a condition known as sepsis, in which widespread inflammation and a compromised blood circulation can result in devastating organ and tissue injuries[3] and impairments to growth and development. On page 407, Panigrahi *et al.*[4] report the results of a clinical trial conducted in rural India to assess whether feeding newborn infants with preparations of health-promoting bacteria can prevent serious bacterial infections and sepsis.

Intensive care and antibiotic treatment are usually, but not always, effective in treating severe sepsis due to bacteria. However, timely antibiotic treatment might not be available in some locations, and antibiotic use can have adverse effects, including decimation of health-promoting gut bacteria and selection for antibiotic-resistant bacteria. There is a continuing need to develop and implement effective sepsis-prevention strategies.

Panigrahi and colleagues tested whether sepsis could be prevented in newborns by orally administering probiotics — live microorganisms that can provide a health benefit — and prebiotics, which are molecules, such as certain carbohydrates in human milk or derived from plants, that are selectively used by host microorganisms and that also confer a health benefit[5] (see also go.nature.com/2vnxtvu). Interventions that combine both probiotic and prebiotic components are known as synbiotics.

Probiotics are among the most studied of all neonatal interventions, and their use in treating premature infants has entered what has been called[6] a 'golden age'. An analysis[6] of 29 clinical trials that had enrolled premature infants of very low birth weight, defined in this context as less than 1.5 kilograms, revealed that probiotics can prevent such infants from acquiring a common and serious gut disease called necrotizing enterocolitis. Another

analysis[7] of 37 trials in premature infants reported that probiotics could prevent a type of sepsis known as culture-positive sepsis, with an overall risk reduction (within the confidence intervals for the data) of 6–22%.

Panigrahi and colleagues' study was in a field-research setting that the authors developed in the Indian state of Odisha, a region classified as in the low to middle tier of sociodemographic development[8]. This setting was well suited for evaluating the benefit of a probiotic-based strategy in a context in which other health-promoting strategies are being used in newborns. Although the study was specifically designed to include infants born in the community, around 85% of the study subjects were born in hospitals, reflecting the increasing use of hospitals for deliveries. In addition, to be eligible for the study, mothers had to have started breastfeeding within the first 24 hours of the infant's life, a practical and effective strategy for reducing the risk of infection. A mother's milk contains prebiotics, as well as other molecules that strengthen gut barriers and immunological defences against pathogens[9].

The authors evaluated a synbiotic preparation given daily for one week to full-term and late-preterm infants, beginning around postnatal day 3. The oral preparation contained the bacterium *Lactobacillus plantarum* — selected from other probiotic candidates because it had previously been shown[10] to have favourable gut-colonizing properties in newborns in this setting — along with fructooligosaccharide, a plant-derived prebiotic[5]. This well-conducted double-blind trial, with a placebo control, began to enrol infants in 2008 and is the first to examine whether a probiotic-based preparation can prevent sepsis in a large sample consisting mainly of full-term newborns.

There is no consensus definition of sepsis. To measure the incidence of the condition, community health workers checked the infants daily for the presence of one of seven signs of possible severe bacterial infection recommended by the World Health Organization as criteria[11] to facilitate early referral, diagnosis and treatment of young infants[12,13]. For an infant to be counted as having sepsis, a physician had to confirm that one of the seven signs was present and conclude that the infant required hospitalization and antibiotic treatment for five days or more. Because such cases occurred later than postnatal day 3, they are termed late-onset cases[3]. The sepsis cases were classified into one of three categories: lower-respiratory-tract infection (such as pneumonia), culture-positive sepsis and culture-negative sepsis. The latter two categories respectively refer to whether or not laboratory tests detected bacterial pathogens in the blood or cerebrospinal fluid.

The authors report that synbiotic treatment significantly lowers the number of late-onset sepsis cases during the first two months of life, the time frame monitored in the trial. The study was terminated in mid-2012, only about halfway to the target enrolment size, on the independent recommendation of the board providing study oversight, because the interim results were convincingly in favour of the synbiotic preparation relative to the placebo. Such interim cessation is standard practice in well-designed studies when analysis reveals such large differences between the study and control groups that it becomes unethical or wasteful to continue to enrol further participants.

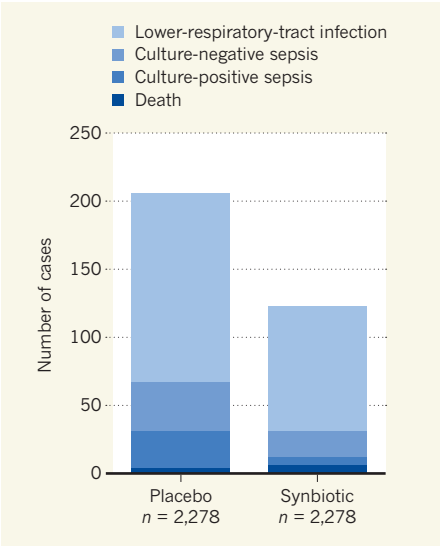

Figure 1 | A clinical trial to prevent sepsis. Panigrahi *et al.*[4] conducted a randomized clinical trial in rural India to assess whether feeding newborns a daily dose of a probiotic strain of the gut bacterium *Lactobacillus plantarum* and a carbohydrate that promotes healthy bacteria — a combination known as a synbiotic — for one week affected the incidence of a serious inflammatory condition called sepsis. Outcomes, including death and the occurrence of three types of sepsis, were monitored for 2 months in 4,556 infants who were randomly assigned to either a group receiving placebo or one receiving the synbiotic preparation. Sepsis or death occurred in 9.0% of the placebo group compared with 5.4% of the infants in the synbiotic group — a reduction of 40%.

Panigrahi *et al.* found that synbiotic treatment reduced the risk of sepsis or death by an astonishing 40%, from 9.0% in the placebo group to 5.4% in the synbiotic group (Fig. 1). Taking into account the margins of error of this estimate, the relative risk reduction could be anywhere from about 25% to 50%. Substantial reductions were seen in all three subtypes of sepsis assessed, and reductions were also observed in diarrhoea and umbilical-stump infection in infants who had not been classified as having sepsis. These striking results demonstrate that the substantial protective effects of probiotics observed in preterm infants[6] also occur for full-term newborns — a much larger segment of the infant population, and one that bears a sizeable proportion of the infectious-disease burden[1].

That a probiotic and prebiotic combination selected to promote gut health would also reduce the incidence of pneumonia is surprising, but not implausible, particularly in light of emerging proposed links between gut microbes, the immune system and lung disease[14]. Nevertheless, more research will be needed to discover and understand the various mechanisms by which gut bacteria affect human health.

Before the study was launched, the investigators and associated community members established a well-developed clinical and research infrastructure in which to conduct preliminary studies to evaluate and select a strong candidate intervention for investigation. The resources necessary for a definitive assessment of the intervention were committed. Too often, interventions that might plausibly benefit many people are judged to be failures on the basis of under-resourced studies involving too few participants. The estimated effects of an intervention in such studies have large margins of error that prevent definite conclusions being drawn from the findings. The work by Panigrahi and colleagues exemplifies how intervention research should be done. Moreover, the trial provides evidence for the effectiveness of a global health intervention that could be used to complement existing strategies for giving every newborn the best chance to survive and thrive. ■

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