We welcome the presentation of data from Oliveira and colleagues. The authors are to be congratulated for their careful analysis, precise standardisation, refusal to over interpret the data, and the caution of their conclusions. The question of whether the risk of microcephaly (and congenital Zika syndrome) after infection with Zika virus during pregnancy varies according to setting is important. We must wait for evidence from the rigorous setting of the cohorts.

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Procalcitonin-guided antibiotic stewardship from newborns to centennials

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In 1993, Assicot and colleagues[1] reported in *The Lancet* that procalcitonin was a marker of systemic infections in neonates and paediatric patients. In 2004, Christ-Crain and colleagues[2] reported that procalcitonin guidance substantially reduced antibiotic use in adult patients presenting to the emergency room with lower respiratory tract infections, and in 2010, Bouadma and colleagues[3] reported that a procalcitonin-guided strategy to treat suspected bacterial infections in non-surgical adult patients in intensive care units reduced antibiotic exposure and selective pressure with no apparent adverse outcome. In 2016, the Stop Antibiotics on guidance of Procalcitonin Study (SAPS)[4] found a reduction of duration of treatment and, importantly, a decrease in mortality in critically ill adult patients with presumed bacterial infection. In 2017, *The Lancet* now reports data of a landmark study done in neonates—the Neonatal Procalcitonin Intervention Study (NeoPInS).[5] In a group of 1710 neonates from high-income countries with low incidence of proven early-onset sepsis, a standardised risk assessment protocol for suspected early-onset sepsis with procalcitonin-guided decision making reduced the duration of antibiotic therapy by around 20% (in the intention-to-treat [ITT] analysis this was 55·1 *vs* 65·0 for the procalcitonin [PCT] group, and in the per protocol [PP] analysis 51·8 *vs* 64·0 h; p<0·0001), and the length of hospital stay by around 5% (in the ITT analysis this was 123·0 h *vs* 126·5 h for the PCT group; p=0·002, and in the PP analysis 115·8 h *vs* 121·0 h for the PCT group; p=0·037). The authors are to be commended for conducting this pragmatic and international, multicentre trial.

As a pragmatic study there are limitations, which were adequately addressed by the authors. The diagnosis of sepsis in neonates is difficult, ambiguous in the absence of a gold standard, and the infection risk distribution of the population studied has an influence on the non-inferiority aspects. These limitations, however, do not preclude the conclusions drawn.

When withholding potentially life-saving antibiotic therapy by any means and in any age group and

clinical setting, safety must be our primary concern. Non-inferiority for re-infection and death was not shown in the NeoPInS study due to the low number of events. However, others have reported reduced mortality associated with procalcitonin guidance of antibiotic therapy in adults, in a large intensive care unit trial[4] and reduced treatment failure due to optimised therapy in a patient data meta-analysis[6] from 4221 patients with respiratory infection.

What do we know about the molecular mechanisms underlying procalciton release and action during infections? In systemic infections, calcitonin (CALC) genes are ubiquitously expressed in parenchymal cells and, in essence, the entire body becomes an endocrine organ.[7] Procalcitonin, a *CALC-I* gene product, is stimulated synergistically by the inflammatory mediators of host response (eg, interleukin 1β, tumour necrosis factor α, and interleukin 6), bacterial products (eg, lipopolysaccharide, lipotechoic acid), and necrotic body cells.[8,9] Production and release of procalcitonin typically occurs after external infection with bacterial microorganisms. Bacterial translocation across the gut wall by gastrointestinal malperfusion could trigger a similar cascade, which explains why circulating procalcitonin increases both during septic and cardiogenic shock.[10] Cellular upregulation of procalcitonin is attenuated by cytokines released in response to viral infections, such as interferon-gamma.[8]

Procalcitonin is the prototype of a hormokine mediator, which shares biological characteristics of both hormones and cytokines.[11] Procalcitonin's kinetic profile shows an increase within 6–12 h of infection and circulating procalcitonin levels are cut in half daily when the infection is controlled.[12] Historically, calcitonin peptides were held responsible for calcium homoeostasis and bone metabolism. However, this is of at most minor biological relevance. The main role of these peptides is seen in the adaption of metabolism and vascular tone during inflammation,[9,13] to combat invading microbes during exogenous infections; and to modulate cytokine release, migration, and phagocytic activity of neutrophils.[14] The several 100 000-times increased procalcitonin levels antagonise the action of other members of the calcitonin peptide superfamily—ie, calcitonin gene-related peptides such as calcitonin-related peptide I and II, adrenomedullin, and amylin.[15] Administration of procalcitonin to septic hamsters with peritonitis doubled their death rate,[16] while treatment with antiserum reactive against calcitonin precursors increased survival in monomicrobial and polymicrobial sepsis in three animal models (hamster, rats, and pigs).[17–19]

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As a diagnostic biomarker, procalcitonin is an objective, dynamic, and easily measurable tool. However, test results can be ambiguous, with false-positive or false-negative results. Physicians should never make decisions based upon one isolated finding, but rather on the overall picture of the patient's illness. Clinical examination and reasoning is essential to determine the pre-test probability of a disease (ie, prevalence), of treatment failure, or of complication for adequate interpretation of laboratory test results. Cutoff ranges are preferred to overly simplistic dichotomous cutoffs. In immunocompetent adults, a high specificity and a high positive predictive value (eg, a procalcitonin level of ≥0·25 to 0·5 ng/mL) is preferred to rule in a disease and to start antibiotic therapy in respiratory tract infections. Conversely, a high sensitivity and a high negative predictive value is needed to "rule out" a disease (eg, a procalcitonin level of <0·1 to 0·25 ug/L) to withhold antibiotic therapy in infections of the respiratory tract. The cutoff ranges proven to be useful in adults are too low for children with a more reactive immune system.[20] In newborns, there is a physiological rise, up to 10 ng/mL within the first 24 postnatal h, presumed to be associated with intestinal bacterial colonisation.[21] The interpretation

of procalcitonin values in neonates is further complicated by an increase due to perinatal factors, such as chorioamnionitis, perinatal asphyxia, and maternal pre-eclampsia.[22] Nevertheless, if the cutoff is adapted accordingly and embedded in a reasonable clinical algorithm—as done in the NeoPInS study—procalcitonin can and should be used to improve antibiotic stewardship.

In the absence of a gold standard for the diagnosis of infection and patients presenting with ambiguous clinical signs, antibiotic decisions are often more dependent on beliefs and the experience of physicians than objective parameters. In NeoPInS, as well as in studies performed in adults,[23] the duration of antibiotic therapy depended largely on the participating centre and local standards of care. Algorithm compliance, or lack thereof, is a direct reflection of the confidence level of physicians in the interpretation of the meaning of serum procalcitonin levels. In two large Swiss studies,[24,25] enforcement of and compliance with the procalcitonin-guided antibiotic algorithm was highest, up to 90%. If the algorithm was enforced, antibiotic exposure was 50–75% lower than in the control group. This effect size is remarkable considering the low overall antibiotic use in Switzerland.

Routine laboratory tests are often ordered without effect on diagnostic or therapeutic management. The NeoPInS study shows how physicians should act upon procalcitonin levels in the context of neonates with suspected early-onset sepsis, with proven benefit for patients in regard to antibiotic treatment and clinical outcome.

In summary, although far from being a perfect marker, procalcitonin is the most reliable of the currently known circulating markers of systemic bacterial infections (sepsis). Procalcitonin-guided antibiotic de-escalation therapy is evidence-based and state-of-the-art for antibiotic therapy for suspected and proven bacterial infection in different clinical settings and different acuity of infections. We now have an evidence base for all age groups, from neonates to centennials. The hypothesis that hormokines like procalcitonin are not only biomarkers mirroring course of infection, but share a pivotal role in the pathophysiology and as such should be the primary therapeutic research target in sepsis, is at the least attractive and at best intuitively obvious.

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My Germany in 2017: a resilient country that is taking responsibility

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2017 is a good year to put a spotlight on Germany and health. Germany is leading the forthcoming G20 meeting and has a general election on Sept 24. The political landscape is shifting palpably given President Donald Trump in the White House, the UK's decision to leave the European Union, and a newly hopeful and energised France under President Emmanuel Macron. After a frustrating G7 meeting in Taormina, Italy, on May 26 and 27, Germany's Federal Chancellor Angela Merkel stated in an unusually blunt speech that as Europeans "we should really take our fate into our own hands…the times in which we could rely fully on others are somewhat over".[1] Germany clearly is in a new leadership role that it has been reluctant to take in the past. The two papers in this *Lancet* Series look at the German health system and its remarkable resilience through a very turbulent time over the past 135 years and Germany's expanding role in global health.[2,3] Leading the G20 Summit in Hamburg on July 7 and 8, Germany has taken important and more assertive steps to show leadership in global health by putting health firmly on the G20 agenda and holding the first ever meeting of G20 Health Ministers in Berlin on May 19 and 20. The declaration by the G20 Health Ministers has a strong focus not only on combating antimicrobial resistance, but also on health systems strengthening for universal health coverage, data systems strengthening for health policy, and building and maintaining a skilled and motivated health workforce as an integral part of functioning and resilient health systems.[4]

My Germany has changed beyond recognition from the place where I grew up in the 1960s, 1970s, and 1980s. It's a good change, one that I am proud of, especially now that my chosen country frequently refers to me as a non-UK born European migrant and I am still awaiting news on what will happen to me in the future 1 year after the Brexit referendum. I have now lived nearly as long in the UK, working first as a medical doctor in paediatrics and then as a medical editor at *The Lancet*, as I have in my home country Germany, where I grew up and went to medical school. What has not changed much is the way the German health system works as the first paper in this Series

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German Federal Chancellor Angela Merkel and German Family Affairs Minister Katarina Barley with participants of the Youth 20 Dialogue, in Berlin, June 7, 2017