Comment

Bacterial meningitis: more can be done

Meningitis remains a substantial cause of mortality and morbidity worldwide and this is particularly true for bacterial meningitis. The big three pathogens—*Haemophilus influenzae* type b, *Neisseria meningitidis* (meningococcal), and *Streptococcus pneumoniae* (pneumococcal)—are responsible for a considerable share of endemic and epidemic meningitis globally. Fortunately, all three of these pathogens are vaccine-preventable. However, in The Lancet Neurology, the GBD 2016 Meningitis Collaborators now show both gains and shortfalls in the efforts to control these sources of meningitis, assessing epidemiological trends using data from the Global Burden of Diseases, Injuries, and Risk Factors (GBD) study from 1990 to 2016.

trial, only 534 (7%) of 7213 patients were reported to have PFO. This proportion means that the remaining 33% of potential patients with PFO were included in the no PFO cohort and, therefore, the patients in whom PFOs were detected might represent a selected rather than an average PFO population. When transoesophageal echocardiography was used, PFO was documented in 379 (27%) of 534 patients. There were no records about whether a bubble test was done in all of these patients and, hence, PFOs might have been missed in some. However, this representative percentage of PFOs might reassure readers about the meaningfulness of the fact that the number of recurrent strokes over 11 months in patients with PFO was reduced by approximately half with rivaroxaban versus aspirin (seven versus 13 events). Admittedly, this finding was not statistically significant. Nonetheless, it would be a mistake to focus solely on the p value instead of considering the whole clinical picture.

Non-randomised comparative studies and randomised trials of PFO closure had shown numerical reductions in stroke risk of up to 80%, but these were not statistically significant, mostly for technical issues (eg, lack of statistical power due to small patient numbers and insufficient follow-up time). Rather than recommending PFO closure, or at least offering it as a non-inferior alternative to lifelong oral anticoagulation or antiplatelets (which have been shown to be inferior), PFO closure with a device has been discouraged until data for long-term follow-up were available. The meta-analysis done by Kasner and colleagues provides an additional example of how a numerically different but non-significant result, when similarly present in several studies, should not be overlooked when exploring optimal treatments for a patient at risk of recurrent ischaemic stroke.

Calling for additional randomised trials with suboptimal treatments in control groups (such as aspirin to prevent recurrent strokes) raises ethical concerns. Instead, we should read the writing on the wall: the findings from the trial by Kasner and colleagues and previous similar trials allow us to draw several general conclusions. First, taking all the evidence into account along with common sense, in patients with a stroke and PFO as the presumed cause, PFO closure with a device should be considered first, oral anticoagulation (eg, with rivaroxaban) second (due to the accumulating bleeding risk), and aspirin should not be considered at all. Second, PFO should no longer be subsumed under ESUS, but classified as a common cause of stroke in the same way as atrial fibrillation.

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The GBD is a comprehensive database that provides estimates on death and disability due to hundreds of causes for 195 countries, with data broken down by age groups, sex, and Socio-demographic Index. The findings of this analysis are intriguing. The successful control of *H influenzae* type b meningitis through aggressive and thorough vaccination campaigns was evident in a 49·1% decrease in incidence of this type of meningitis, going from the highest among the three causes of incident meningitis in 1990 to the lowest in 2016. This decrease shows the successes of organised and targeted vaccine implementation initiatives worldwide. Similarly promising, the overall global number of deaths due to meningitis decreased by 21·0% between 1990 and 2016. However, this fact is bittersweet: during the same period, the decreases in death rates from other vaccine-preventable diseases, such as measles (a 93% decrease) and tetanus (91% decrease), dwarf the progress made in preventing deaths from meningitis. Incidence of and deaths due to pneumococcal meningitis (the largest cause of years of life lived with disability among survivors) decreased over time, again attributable to increased widespread availability of polyvalent pneumococcal vaccines. Pneumococcal conjugate vaccines can result in herd immunity by preventing nasopharyngeal carriage of the bacteria targeted by the vaccine, although bacteria not covered by the vaccine are not affected, highlighting the need for continued work on even more multivalent pneumococcal vaccines.

Most meningitis deaths occurred in the meningitis belt—a region roughly covering a swath of sub-Saharan Africa stretching from Senegal in the west to Ethiopia in the east. This region is marked by periodic large outbreaks of meningococcal disease, mainly meningococcus A (MenA). Efforts to implement widespread vaccination for MenA, principally through the MenAfriVac programme, have led to declines; as of 2017, 21 countries in the meningitis belt had implemented vaccination in people aged 1–29 years, and the remaining few are near completion. However, only a minority of countries have implemented the MenA vaccine into their routine expanded programmes on immunisation for children. Additionally, epidemics due to MenC, MenW, and other meningococcus serogroups continue to occur, highlighting the need for more multivalent meningococcal vaccines to control epidemics in the meningitis belt.

Perhaps paradoxically, overall incident meningitis cases increased over the assessment period, going from 2·50 million in 1990 to 2·82 million in 2016. Similar to deaths from meningitis, incidence was highest in the meningitis belt; it was also highest in neonates. This increase in incidence appeared to be driven by the category of other meningitis causes (a term used by the GBD 2016 Meningitis Collaborators as a catch-all for other forms of bacterial, fungal, and viral meningitides). This categorisation is a limitation of the study because it fails to provide specific data for other major causes of meningitis, including group B Streptococcus, *Listeria monocytogenes*, nosocomial meningitides, and of course viral (aseptic) meningitis, which can still result in substantial morbidity long-term. The collaborators do provide reassurance, however, that efforts to separate out these other causes of meningitis are underway, which should increase the robustness of future data.

The GBD 2016 Meningitis Collaborators astutely note barriers to the control of meningitis in resource-limited areas, including limited capacity for CSF analysis, the challenge of making a clinical diagnosis of meningitis in neonates and young children, and limitations in laboratory diagnostics that can be done on site. In addition to the focus on implementing aggressive vaccination campaigns, attention should be paid to addressing these other challenges.

Overall, great strides in control of three of the most important causes of meningitis worldwide have been made. But as the GBD 2016 Meningitis Collaborators show, substantial challenges remain to the control and prevention of bacterial meningitis, particularly in the meningitis belt. As evidenced by the data from this study, the medical community and government agencies should—and can—do better by strengthening health system infrastructure, developing more effective vaccines, wider implementation of these vaccines, and eliciting greater advocacy for implementation of these measures by stakeholders.

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Global burden of motor neuron diseases: mind the gaps

According to the International Classification of Diseases ninth (ICD-9) and tenth (ICD-10) editions, the category of motor neuron diseases comprises amyotrophic lateral sclerosis, progressive muscular atrophy, primary lateral sclerosis, progressive bulbar palsy, spinal muscular atrophy, and hereditary spastic paraparesis. Spinal muscular atrophy and hereditary spastic paraparesis have a genetic basis, whereas amyotrophic lateral sclerosis, progressive bulbar disease, and primary lateral sclerosis, all of which are adult forms of motor neuron disease, have both familial and sporadic forms. Spinal muscular atrophy is a disease of infancy and childhood, hereditary spastic paraparesis often presents in childhood, and the remaining forms of motor neuron disease occur mostly in people aged older than 50 years. All motor neuron diseases are rare (rare diseases are defined by a prevalence of <1 per 2000 population in Europe), and obtaining sufficient data to generate a global burden for all motor neuron diseases is challenging. By systematic analysis of all available data between 1990 and 2016, from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2016 now reported in The Lancet Neurology, the GBD 2016 Motor Neuron Disease Collaborators have provided the first report of the burden of motor neuron diseases for 195 countries and territories.

Calculating the burden of motor neuron disease for European populations is straightforward. European population-based registers report consistent incidence rates (2–3 per 100 000 person-years) of amyotrophic lateral sclerosis. Population-based data for individuals of non-European descent are sparse, but incidence rates might be lower in Asia (0·7–0·8 per 100 000 person-years) than European populations. The incidence of spinal muscular atrophy varies across populations. This variation is most probably a function of different carrier rates of the disease-causing variants of the SMN gene across different ancestral populations, whereas the reasons for the geographic variations in incidence of amyotrophic lateral sclerosis are unclear.

Amyotrophic lateral sclerosis is a complex genetic disorder, and analysis of data from population-based registers suggests that disease pathogenesis is a six-step process. The number of steps is reduced for people carrying a known disease-causing variant, such as a hexanucleotide expansion in C9orf72 or a pathogenic mutation in SOD1. The frequencies of these mutations vary across ancestral populations, but this variability does not fully account for the non-uniform geographical distribution, as known familial amyotrophic lateral sclerosis accounts for only 10–15% of all cases.

Being of mixed ancestry might be protective in sporadic disease, as a population-based study of mortality in Cuba revealed rates that were lower in the mixed population (0·55 per 100 000 person-years) compared with those primarily of Spanish or African origin (about 0·9 per 100 000 person-years).

Using all available data, the GBD team have now estimated the years of life lost (YLLs), years of life lived with disability (YLDs), and disability-adjusted life-years (DALYs) associated with motor neuron diseases. The number of people with motor neuron diseases is increasing, but this is mostly attributable to population ageing. The burden of motor neuron diseases is mainly attributable to amyotrophic lateral sclerosis, and is highest in countries with high Socio-demographic Index (SDI; a composite measure of income per capita, education, and fertility), including countries in high-income North America, Australasia, and western Europe; this finding is unsurprising because health services are well developed and provide high standards of clinical care. Age-standardised incidence rates of motor neuron diseases within 10-year age groups are varied, with the age groups of 70–79 years, 80–89 years, and ≥90 years contributing most to the burden of disease.