**Invasive meningococcal disease as a cause of sudden and unexpected death in a teenager: the public health importance of confirming the diagnosis**

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Dear Editor,

We read with interest the article in this Journal by Hong et al., who describe the clonal replacement and expansion of a hypervirulent strain of group W *Neisseria meningitidis* (MenW) belonging to the ST11 clonal complex (cc11) in France, which was associated with a high case fatality rate (CFR) [1]. Invasive meningococcal disease (IMD) is notorious for its sudden onset and rapid progression to life-threatening infection and death [2]. In adolescents and young adults, where the condition can mimic other illnesses, such as influenza, food poisoning, drug misuse or alcohol intoxication, the diagnosis of IMD may not be considered by clinicians in the acute stages of the illness. Where IMD is suspected, antibiotic administration prior to hospital transfer or prior to performing blood cultures increases the likelihood of negative bacterial cultures and, therefore, missing the aetiology [3]. The diagnosis of IMD might also be missed in cases with a rapidly progressing illness resulting in sudden death outside the hospital setting, where the condition of the patient prior to death might not have been witnessed. We were recently involved with such a case, who was diagnosed with IMD four months after death, and would like to highlight the clinical and public health importance of ascertaining this rare but important diagnosis, even at post-mortem.

An 18-year old first-year university student recently developed mild headache on a Friday, which worsened on Saturday although the case was well enough to attend a concert that evening. The case returned to the family home around midday Sunday, ate lunch and slept in the afternoon, but woke up reporting cold hands and feet at 18:00 and stomach ache with vomiting at 23:00, 02:00 and 04:00. The case’s parents contacted the out-of-hours doctor and a clinical diagnosis of acute food-poisoning following chicken consumption at the concert was made during the telephone consultation. A plan was made for medical review at the case’s home, which occurred at 05:30. At this point, the case was seriously unwell. Intramuscular benzylpenicillin was administered immediately and the case was transferred by ambulance to the hospital. The case developed septic shock, continued to deteriorate rapidly and passed away at 10:00 on the same day.

A post-mortem was performed four days later but only toxicology samples were taken for analysis. Three months later, the coroner reported the cause of death as unascertained. Despite the clinical history being consistent with serious bacterial infection, a drug-related cause of death was suspected because of the age of the case. It was only after the parents contacted a national meningitis charity that it became apparent that testing for meningococcal disease (or any other infectious disease) had not been undertaken at the hospital or during post-mortem investigation. After extensive discussions with the coroner, four stored post-mortem blood samples were retrieved from the local hospital and sent to the Public Health England (PHE) Meningococcal Reference Unit (MRU) for PCR-testing. A diagnosis of group W IMD was confirmed within two days of sample receipt.

Infection is known to be a rare cause of death in healthy teenagers and young adults [4], in contrast to drug use and drug dependence, which are recognised as common causes of early death. Death due to drug misuse occurs when the underlying cause is (a) drug abuse or drug dependence; or (b) drug poisoning and where any of the substances controlled under the Misuse of Drugs Act 1971 are involved [5]. In England and Wales, drug poisoning was responsible for 1 in 6 deaths among people in their 20s and 30s in 2016 [4]. During 2016, there were 2,153 recorded deaths in 15-24 year-olds (1,487 male, 69%) and 1,244 (966 male, 78%) were due to ‘External causes of morbidity and mortality’ [6].

Death due to IMD is rare, especially in teenagers. In England, during 2014/15-2016/17, there were 368 IMD cases (138 cases in 2016/17; incidence, 1.8/ 100,000) and 23 deaths recorded on the death certificates among 15-24 year-olds (case fatality rate 6%, equivalent to an annual mortality rate of ~1 per million). Additionally, enhanced national IMD surveillance through PHE identified only four additional IMD-associated deaths in 15-24 year olds over the same three-year period.

Whilst recognising that drug use and drug dependence are leading causes of death in teenagers and young adults, it is important to consider an infectious cause, especially when infection-related symptoms precede the death, even if there is a history of social activity or behaviour which may increase suspicion for drug misuse, such as clubbing, recent recreational drug taking or alcohol consumption, which is common in this age-group. New university entrants, especially those in halls of residence, have a >10-fold higher risk of developing IMD compared to those in the same age-group who are not attending university [7].

 Early recognition of IMD cases is important:

* So that families are appropriately and accurately informed without undue delay.
* To ensure timely and appropriate public health actions to minimise the short-term and long-term risk in close contacts of the case, including rapid antibiotic chemoprophylaxis and vaccination where appropriate;
* To facilitate monitoring of outbreaks through disease surveillance; timely identification of an outbreak could potentially lead to implementation of mass chemoprophylaxis with or without vaccination to prevent further cases from occurring.
* To ensure that any specific characteristics of circulating strains are identified so that clinicians can be informed, such as group W disease and gastrointestinal presentation [8].

Whilst drug misuse remains the most important cause of sudden and unexpected death in teenagers and young adults, other causes, especially those related to infection, should be considered. In particular, confirming IMD is critical because of potential clinical and public health implications for the family and the wider community. Since administering antibiotics prior to taking microbiological specimens is likely to yield negative bacterial cultures, additional investigations such as molecular testing, including PCR-testing for IMD and other infectious diseases, should be routinely performed in all fatal cases where the cause of death is not ascertained.

* **Consent for publication:**

Written informed consent was obtained from the parent of this patient for publication of the case report

* **Competing interests**

HC, CA, MR and SL have no personal competing interest. MR is a medical advisor and on the research panel for the MRF and MenNow charities respectively. PHE Immunisation and Countermeasures has provided vaccine manufactures with post-marketing surveillance reports which the companies are required to submit to the UK Licensing authority in compliance with their Risk Management Strategy. In accordance with PHE policy a cost recovery charge is made for these reports. RB performs contract research on behalf of Public Health England for GSK, Pfizer and Sanofi Pasteur.

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**REFERENCES**

1. Pace, D. and A.J. Pollard, *Meningococcal disease: clinical presentation and sequelae.* Vaccine, 2012. **30 Suppl 2**: p. B3-9
2. Ragunathan, L., et al., *Clinical features, laboratory findings and management of meningococcal meningitis in England and Wales: report of a 1997 survey. Meningococcal meningitis: 1997 survey report.* J Infect, 2000. **40**(1): p. 74-9.
3. Parikh, S.R., et al., *Epidemiology, clinical presentation, risk factors, intensive care admission and outcomes of invasive meningococcal disease in England, 2010-2015.* Vaccine, 2018.
4. ONS, *Statistical bulletin: Deaths related to drug poisoning in England and Wales: 2016 registrations*, O.f.N. Statistics, Editor. 2017: <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletins/deathsrelatedtodrugpoisoninginenglandandwales/2016registrations>.
5. Office for National Statistics. *ONS Death registrations summary tables - England and Wales 2016*, Office for National Statistics, Editor. 2017: <https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/datasets/deathregistrationssummarytablesenglandandwalesreferencetables>
6. Mandal, S., et al., *Risk of invasive meningococcal disease in university students in England and optimal strategies for protection using MenACWY vaccine.* Vaccine, 2017. **35**(43): p. 5814-5818.
7. Campbell, H., et al., *Presentation with gastrointestinal symptoms and high case fatality associated with group W meningococcal disease (MenW) in teenagers, England, July 2015 to January 2016.* Euro Surveill, 2016. **21**(12)