Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

We need estimates of gonorrhoea vaccine protection and symptomaticity by sex and anatomical site

The reports from Winston E Abara and colleagues[1] and Bing Wang and colleagues[2] on the effectiveness of the 4CMenB vaccine against *Neisseria gonorrhoeae* are important as even a partially protective vaccine could play a key role in tackling the rising incidence of gonorrhoea and the threat of antimicrobial resistance,[3] alongside more sophisticated approaches to prescribing of antibiotics[4]—both currently used[5] and new[6] drugs.

To make the best use of limited public health resources, we need to determine the appropriate groups to be offered gonorrhoea vaccination—eg, men who have sex with men (MSM), female sex workers, and heterosexual adolescents and young adults[7]—noting that, within any broad group selected for vaccination, it is likely to be necessary to devise approaches to focus on individuals at highest risk of infection and onward transmission.[3,8] Decisions regarding which groups to vaccinate need to consider gonorrhoea's natural history (which is currently poorly characterised[3,8,9]) and transmission patterns, the prevalence of antimicrobial resistance (which is usually higher in MSM[4]), the frequency and severity of sequelae in women and men,[8] and the potential effects of vaccination.

Women tend to have the most severe sequelae with *N gonorrhoeae* infection (pelvic inflammatory disease, tubular factor infertility, and ectopic pregnancy), so the health benefits and reduced treatment costs from vaccination of heterosexuals are likely to accrue mostly in women.[7] For the heterosexual population, there are two main options: women-only vaccination or gender-neutral vaccination. Women-only vaccination would require less vaccine and would still provide indirect protection to men by reducing the prevalence of *N gonorrhoeae* infection in their sexual partners. Gender-neutral vaccination would provide greater protection, directly and indirectly, to both sexes, but at greater cost. However, with a partially protective vaccine, it might be cost-effective to vaccinate both sexes, even if the benefits are mostly from protecting women, so that women gain both direct and indirect protection—particularly if coverage is limited by low uptake or restricted targeting of vaccination—hence, modelling analysis is required.

To inform decision making for all groups being considered for vaccination, essential information includes separate estimates of gonorrhoea vaccine protection in women and men and, where possible, estimates by anatomical site of infection,[7,9] as differential protection by site could cause differences in average vaccine protection of individuals in different groups. We encourage those with suitable data, whether from observational studies or trials, to report these estimates. Finally, the proportions of incident infections that are symptomatic are important natural history parameters, which are poorly defined;[3,8,9] these estimates can be provided by cohort studies that have regular testing for asymptomatic infection (including the placebo groups of vaccine trials),[3] and we encourage reporting by sex and anatomical site.

PJW reports payment from Pfizer for teaching of mathematical modelling of infectious disease transmission and vaccination. LKW has consulted for Wellcome Trust. DN declares no competing interests. The views expressed in this Correspondence are those of the authors and not necessarily those of the UK Department of Health and Social Care, EU, Foreign, Commonwealth & Development Office, Medical Research Council, National Institute for Health and Care Research, UK Health Security Agency, or Wellcome Trust.

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COVID-19, haemophagocytic lymphohistiocytosis, and infection-induced cytokine storm syndromes

We welcome the Grand Round by Danielle Steed and colleagues[1] describing bartonella-associated

	Microbe	Key cytokines or chemokines	Targeted therapies
COVID-19 cytokine storm	SARS-CoV-2	IL-6	IL-6 inhibitors (tocilizumab) and JAK inhibition (baricitinib)
Human herpes virus-8-positive Castleman disease	HIV and human herpes virus-8	IL-6 and CXCL-13	IL-6 inhibitors (siltuximab) and B-cell depletion (rituximab)
Primary haemophagocytic lymphohistiocytosis	Various (eg, Epstein-Barr virus and cytomegalovirus)	IFNγ and CXCL-9	IFNγ inhibition (emapalumab) and JAK inhibition (ruxolitinib)
Secondary haemophagocytic lymphohistiocytosis or macrophage activation syndrome	Various (eg, *Mycobacterium tuberculosis*, *Leishmania* parasites, and *Bartonella* spp)	IL-1, IL-6, IL-18, and IFNγ	IL-1 inhibition (anakinra), IL-6 inhibition (tocilizumab), and JAK inhibition (ruxolitinib)

CXCL=CXC motif chemokine. IFN=interferon. IL-interleukin. JAK=Janus kinase.

Table: **Infection-induced cytokine storm syndromes**

haemophagocytic lymphohistiocytosis in an immunosuppressed patient. This paper highlights the broader topic of infection-induced cytokine storm syndromes. Recent research in COVID-19 cytokine storm syndrome and Castleman disease has expanded the concept of pathological immune activation and established important principles applicable to other infection-induced cytokine storms.[2]

First, key cytokines and chemokines driving the pathological process can be identified, and inhibiting these cytokines can improve outcomes (table). For example, interleukin (IL)-6 drives much of the pathophysiology of COVID-19 cytokine storm syndrome and Castleman disease, and inhibition of IL-6 is effective in both diseases. Second, immunomodulation in cytokine storms can be beneficial even in the absence of effective antimicrobial therapies. In the case presented by Steed and colleagues, there were effective treatments for both microbes involved; antiretroviral therapy for HIV and doxycycline for bartonella. By contrast, immunomodulatory therapies, such as IL-6 inhibition and Janus kinase (JAK) inhibition, decrease mortality in patients with severe COVID-19 even without antiviral therapies.[3] Third, although Steed and colleagues are correct in highlighting etoposide and dexamethasone-based therapies as the cornerstone of haemophagocytic lymphohistiocytosis treatment, recent advances in treatment for this disease that parallel treatment of COVID-19 cytokine storm syndrome are worth noting. Emapalumab, an inhibitor of interferon γ (IFNγ), is highly active and has minimal toxicity in paediatric patients with primary haemophagocytic lymphohistiocytosis. Additionally, JAK inhibitors, such as ruxolitinib, can salvage patients with haemophagocytic lymphohistiocytosis associated with infection and malignancy who would otherwise be difficult to treat with chemotherapy.[4]

Finally, the statement that "Bone marrow aspiration has been shown to be the most likely test to lead to recognition of haemophagocytic lymphohistiocytosis"[1] requires a caveat. Although bone marrow aspiration is indeed a very important test in patients suspected of having haemophagocytic lymphohistiocytosis, haemophagocytosis does not always signify the pathological immune activation that defines a cytokine storm. Reactive haemophagocytosis can be seen in a wide variety of conditions, including haemolysis, autoimmune disease, sepsis, and after blood transfusions.[5] Additionally, the presence of haemophagocytosis in the bone marrow is not required for diagnosis of haemophagocytic lymphohistiocytosis if other criteria are met. Specialised tests to help distinguish haemophagocytic lymphohistiocytosis from other conditions, such as flow cytometry for perforin, natural killer-cell cytotoxicity, and T-cell activation profiles, and measurement of serum soluble IL-2 receptor, CXCL-9, and IL-18, are not widely available. Haemophagocytic lymphohistiocytosis is a clinicopathological diagnosis that requires a clinician to combine the available clinical and laboratory evidence to determine that a patient has a pathological immune activation.

LYCC received advisory board fees from EUSA-Pharma, and speakers fees from GlaxoSmithKline, outside of the submitted work. LYCC's research is supported by the Hsu & Taylor Family, a philanthropic fund at the VGH & UBC Hospital Foundation. All other authors declare no competing interests.

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