APAGBI Best practice guidance on immunisation and surgery

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1. Summary

Best practice advice is provided in relation to administration of vaccines to children in the peri-operative period. The basis for this best practice advice is a review of the literature. Aspects considered are vaccine efficacy and the impact of adverse effects of vaccines, there are few areas of strong evidence. There is clear evidence of the role of the routine immunisation schedule in the reduction in mortality and morbidity among infants and children. Attention is drawn to the importance of routine immunisation.

Below is a summary of the key recommendations. The findings of the literature review and information about the vaccines and the vaccine schedules can be found in the following document.

2. Key Recommendations*

1. The routine vaccination schedule should not usually be delayed because of elective surgery, especially in infants.
2. Urgent surgery should not be delayed due to recent vaccination
3. Inactivated vaccines - delay major elective surgery until 48 hours after vaccination because of the potential overlap between surgical complications and adverse effects of the vaccine.
4. Live attenuated vaccines – no need to delay elective surgery but there remains a small possibility that a child may develop a fever at the time of admission for elective surgery and an assessment will be required.
5. Vaccines may be administered after elective surgery after the child has recovered and is well.

***Exclusion – immunocompromised children, for these patients seek expert advice**

3. Table of Contents

4. Introduction

The United Kingdom vaccination schedule continues to expand. The schedule now includes the meningococcal B vaccine and there is the possibility of a COVID-19 vaccine for children in the near future.(1) The Green Book guidance produced by the Public Health England 'Immunisation against infectious disease' states that elective surgery or imminent general anaesthesia should not be a contraindication to routine immunisation.(2) In spite of this guidance the timing of elective surgery can create a dilemma when it coincides with a scheduled vaccination. Different countries have a range of approaches and there is no clear consensus view. (3)(4)(5)(6)(7)(8)(9) Inconsistent local policy and failure to integrate with wider public health initiatives in relation to vaccination can have a significant impact on late cancellation of planned surgery. (10)

Questions raised include whether there should be an interval after a vaccination and the optimal duration of that interval. If an interval is thought to be prudent then which of the 2 interventions, the vaccination or the elective surgery, should be delayed. Consideration of the risks of interruption to the vaccination schedule, the potential effects of vaccination on the surgical outcome and potential effects of surgery and anaesthesia on the efficacy of the vaccination are pertinent. Others have raised the possibility of opportunistic administration of vaccines under anaesthesia. (9)

5. Scope and aims

This best practice guidance aims to review the evidence regarding interactions between recent vaccination, surgery and anaesthesia, with a summary of the effect of anaesthesia on the immune system. Common adverse symptoms following each vaccine are outlined to help

facilitate decision making when considering elective surgery in a recently vaccinated symptomatic child.

6. The importance of vaccination

Immunisation schedules are designed to provide early protection and reduce the risk of vaccine preventable disease. Concern about the interaction between vaccines, surgery and anaesthesia must be balanced with an understanding of the potential impact of disruption and delay to the schedule both for the individual and the wider population.(6) This is important for infants. In later childhood, with booster doses, timing is less critical.(11)

7. The impact of vaccination on surgery

There is no evidence that recent vaccination increases the risk of complications from either surgery or anaesthesia. However sequelae e.g. fever and irritability arising immediately before elective surgery may result in cancellation. (10) Such adverse effects may complicate the assessment of a child in the post-operative period.(11) This is most relevant after elective major surgery.

Adverse effects are most likely to occur in the first 24-48 hours after administration of inactivated vaccines, and up to 3 weeks after live vaccines such as MMR.(12)

The inactivated meningococcal B (4CMenB - Bexsero®) vaccine is now routine in infancy. It can predictably make children acutely unwell with systemic upset ± fever >38.5°C in 50-60% of infants (table 1).(13) Separate studies in the UK have found a small but significant increased rate for attendance at general practices or admissions to hospital for fever after 4CMenB at

2 and 4 months of age, with an associated increase in the number of investigations for bacterial infection.(14,15) Distinguishing between an infant or child with fever caused by recent 4CMenB vaccine and a serious bacterial infection is a clinical challenge. Currently, National Institute for Care and Excellence (NICE) guidelines recommend that all infants younger than 3 months who present with fever (≥38°C) have bloods taken, urine testing and chest x-ray if respiratory symptoms are present.(16) Lumbar puncture (LP) is recommended in the presence of leucocytosis (>15 x 10^9/L), however the presence of leucocytosis has been shown to be 73% in infants presenting with fever following 4CMenB vaccination raising concern that infants will be subjected to unnecessary septic screens, hospitalisations and antibiotic use.(15) Fever that persists beyond 48 hours after vaccination in the infant warrants careful clinical assessment by an experienced clinician.(17) The Joint Committee of Vaccination and Immunisation (JCVI) has recommended that paracetamol should be given prophylactically following the 4CMenB vaccine in infants under one year of age and for up to 48 hours if symptoms persist and the child appears otherwise well.(18) Paracetamol has been shown to decrease fever and reactogenicity with no apparent clinically relevant impact on immune responses to the 4MenB vaccine.(19)

These symptoms attributable to 4CMenB usually resolve within 48 hours and we would therefore continue to recommend delaying elective surgery for at least 48 hours following an inactivated vaccine to avoid diagnostic confusion in the febrile peri-operative child.

Adverse effects may occur up to 3 weeks after a live vaccine but the risk of fever is of a similar magnitude to the background risk of fever in any child presenting for surgery and therefore no delay is indicated before elective surgery.(6)

8. Vaccine efficacy, surgery and anaesthesia - Summary of evidence

There is evidence that anaesthesia and surgery may suppress the immune system in the perioperative period but there is also no evidence that surgery and anaesthesia following a recent vaccine decreases its efficacy. No study has examined either the effect of surgery and anaesthesia on the efficacy of immunisation or the impact of the development of the relevant antibody response in infants and children.(20)

Anaesthesia and surgery can cause direct and indirect immune modulation. Innate and adaptive immunity may be altered because of the detrimental effects on the cellular components involved i.e. natural killer cells (21), dendritic cells, neutrophils (22), macrophages (23) and lymphocytes (24)). Indirect effects of anaesthesia and surgery on the immune response arise as a result of the stress response via hypothalamic-pituitary-adrenal axis, catecholamines and glucocorticoid production. Studies that have investigated the effect of anaesthesia on immune function in children without the associated surgical stress response (e.g. MRI) do not allow robust conclusions to be made.(4)

Exposure to volatile anaesthetics (VA) has generally resulted in a decrease in the number and proliferation of T cells.(25) Various aspects of the adaptive immune response have been shown to be modulated by volatile anaesthetics. CD4, CD8 and T helper cells 1 and 2 have all been shown to be sensitive to sevoflurane and isoflurane induced apoptosis.(26) Building on lymphocytic suppression by VAs, animal models have shown reduced clinical disease of multiple sclerosis following a single exposure to sevoflurane. This is thought to be due to its suppression of T cell activation and proinflammatory cytokine production.(27)

The clinical impact of a short period of immunosuppression on recent immunisation is unclear. Studies of antibody responses to pneumococcal vaccination following splenectomy in adults show a protective response even if given immediately after surgery.(28) Whether antibody response in the perioperative period in post splenectomy patients can be extrapolated to infants and children is unclear. The finding does however, provide indirect evidence against a major inhibitory influence of anaesthesia/surgery on adult vaccine responses.(4) The evidence that does exist suggests that the transient surgery immune modulation appears to return to preoperative values within approximately 2 days.

9. Opportunistic vaccination

It has been suggested that the surgical episode provides an opportunity to administer vaccines to patients who have missed scheduled vaccinations. (9) This is not recommended for children who are able to receive the vaccine in the usual manner. If the vaccine can only be administered under anaesthesia, e.g. in the setting of anxiety and behavioural disorders where administration of vaccine has not been possible, then the benefits of achieving vaccination outweigh concerns about the impact of anaesthesia on vaccine efficacy.

10. SARS-CoV-2

At the time of writing three vaccines have been authorised in the UK, the Pfizer BioNTech, Moderna and the AstraZeneca COVID-19 vaccines. There are some safety data on the Pfizer BioNTech vaccine in children aged 12 years and older. The JCVI have set out a prioritisation for persons at risk. 16-18 year olds may receive the SARS-CoV-2 vaccine if they are in groups 4 (clinically extremely vulnerable) or group 6 (a designated at risk group).

The AstraZeneca and Moderna COVID-19 vaccines are only licensed from 18 years of age but JCVI have recommended that it can be used in those aged 16-17 years if the Pfizer BioNTech vaccine is not available. (1)

Children and young people have a very low risk of COVID-19, severe disease or death due to SARS-CoV-2. At the time of writing this guidance SARS-CoV-2 vaccine trials have begun in children. (1) In the absence of sufficient safety and efficacy data COVID-19 vaccines are not currently recommended for children and young people under 16 years of age. Limited data suggest that children with neurological comorbidities may be at a greater risk of developing severe COVID-19. (1) Vaccination may be considered for children with severe neuro-disabilities in specialised residential care settings. (1) Vaccination of at risk older children in these settings may be undertaken using any of the approved vaccines. Use of the current vaccines below the age of the authorisation in children at high risk is in line with the advice of JCVI as "off-licence" use.(1) Current guidance is that scheduling of COVID-19 vaccination should be separated, by an interval of at least 7 days, from co-administration of any other vaccine to avoid incorrect attribution of potential adverse events. (1)

The Royal Colleges of Surgeons have advised that adult elective surgery essential urgent surgery should take place, irrespective of COVID vaccination status and that non-urgent elective surgery can also take place soon after vaccination. An interval between surgery and vaccination of a few days (at most 1 week) is suggested. This is to allow any symptoms such as fever to be correctly attributed to either vaccination or the operation itself.(29)

11. Adverse effect profiles

Table 1. Common adverse effects following vaccines(1,30–35)

Vaccine	Common side effects
Meningococcal B (4CMenB - Bexsero®)	Fever (≥38°C), irritability (71%), diarrhoea (23%), vomiting (26%), reduced feeding (63%) drowsiness, unusual crying, subcutaneous nodule at the injection site that can last persist for up to several months, development of rash in infants and children up to ten years of age.(17) In infants and children under 2 years, fever ≥38°C (occasionally ≥39°C) is more common when 4MenB is administered at the same time as routine vaccines than alone. Fever peaks at 6 hours and is usually gone by 48 hours post vaccination. Paracetamol for symptomatic relief is no longer contraindicated and prophylactic use is recommended.(18,19,36,37)
Pneumococcal conjugate vaccine (PCV) PCV 13 (Prevenar13®) and Pneumococcal polysaccharide vaccine 23 (PPV23)	In children 6 weeks to 5 years of age PCV13 – fever, irritability, decreased appetite, increased and/or decreased sleep. PPV23 – less commonly low grade fever.
6 in 1 vaccine (DTaP, IPV, HiB, HepB)	Fever, pain.
Rotavirus (Rotarix®)	Diarrhoea, irritability, vomiting, abdominal pain, flatulence, skin inflammation, regurgitation of food, fever and loss of appetite.
Influenza (Fluenz Tetra® live attenuated, Flucelvax®Tetra quadrivalent cell cultured inactivated vaccine (QIVc))	Low grade fever, malaise, shivering, fatigue, headache, myalgia and arthralgia.
Meningococcal C (MenC) conjugate	Mild fevers, crying, irritability, drowsiness, impaired sleep, reduced appetite, diarrhoea, vomiting, headaches, myalgia.

Haemophilus B/MenC conjugate (Menitorix®)	Irritability, loss of appetite, slightly raised temperature.
Quadrivalent (ACWY) conjugate (Menveo® and Nimenrix®)	Headache, nausea, rash, malaise, irritability, drowsiness, loss of appetite.
MMR(38)	Malaise, fever and/or rash may occur, most commonly about a week following immunisation, with a duration of two to three days. Parotid swelling in 1% of children aged under 4, usually in the third week. Adverse reactions (except anaphylaxis) are due to effective replication of the vaccine virus with subsequent mild illness. Events due to the measles component occur 6 to 11 days after vaccination, mumps and rubella two to three weeks after vaccination but can be up to 6 weeks. Less common after second and subsequent doses.
Human papilloma virus (HPV) vaccine	Headache, myalgia, fatigue and low grade fever.
Tuberculosis (Bacillus Calmette-Guerin-BCG)	Expected reaction to successful BCG vaccination, seen in 90-95% of recipients, is induration at the injection site followed by a local lesion. Headache, fever and enlargement of a regional lymph node can also occur.
Pfizer BioNTech COVID-19 mRNA Vaccine BNT162b2 (data from trial participants 16 years and older)	Injection site pain (>80%), fatigue (>60%), and headache (>50%). Myalgia, arthralgia and chills were also common with fever in 10-20%, mainly after the second dose. Lymphadenopathy was reported in less than 1%.
Moderna mRNA-1273 COVID-19 vaccine (data from trial participants 18 years and older)	Localised pain at the injection site (>75%), mild systemic effects including headache, fatigue, joint and muscle aches and chills. Fever usually after second dose.
AstraZeneca COVID-19 vaccine (data from trial participants 18 years and older)	Mild pain and tenderness at the injection site, fatigue and headache were also common. Mild fever (>38°C) was recorded in the first 48 hours for around a quarter of younger participants

12. Immunisation schedule (39)

Infants

Vaccine	Age	Notes
6 in 1 vaccine (Infanrix hexa®) Rotavirus MenB	8 weeks	Diphtheria, tetanus, acellular pertussis (DTaP), hepatitis B (HepB), haemophilus influenzae type B (HiB), inactivated polio virus (IPV). Inactivated. Oral vaccine, live attenuated. Likely to develop high temperature within 24 hrs of vaccination. Inactivated.
6 in 1 vaccine (2nd dose) Pneumococcal vaccine (PCV) Rotavirus (2nd dose)	12 weeks	Inactivated
6 in 1 vaccine (3rd dose) MenB (2nd dose)	16 weeks	

Children aged 1 to 15

Vaccine	Age	Notes
HiB/MenC, MMR, PCV (2nd dose), MenB (3rd dose)	1 year	HiB/MenC Inactivated MMR Live attenuated
Flu vaccine – (every year between October and January)	2 to 10 years	Nasal spray, (Fluenz Tetra®). Live attenuated, inactivated available if child in clinical risk group
MMR (2nd dose) 4 in 1 pre-school booster	3 years and 4 months	DTaP, IPV. Inactivated
HPV vaccine	12 to 13 years	
MenACWY – Nimenrix® 3-in-1 teenage booster	14 years	Inactivated Tetanus, diphtheria (Td) and IPV. Inactivated

Other live vaccines - Shingles, BCG, oral typhoid, varicella, yellow fever

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