Vaccine 37 (2019) 539–549

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Review

Would immunization be the same without cross-reactivity?

Ivo Vojtek [a,*], Philippe Buchy [b], T. Mark Doherty [a], Bernard Hoet [a]

[a] GSK, Avenue Fleming 20, 1300 Wavre, Belgium
[b] GSK, Singapore, Singapore

ARTICLE INFO

Article history:
Received 21 August 2018
Received in revised form 7 November 2018
Accepted 4 December 2018
Available online 24 December 2018

Keywords:
Vaccines
Cross-reactivity
Cross-protection
Adjuvants

ABSTRACT

"Cross-reactivity" (the observed immune response against pathogen types not specifically targeted by the vaccine antigen composition) and "cross-protection" (clinical protection against related non-vaccine microorganism types) are vaccinology concepts that are attracting renewed interest in the context of disease prevention. National health authorities are collecting mounting evidence of the importance of cross-reactivity. For some vaccines, this has been substantiated by cross-protection data from clinical studies and/or post-licensure data, where their introduction into immunization programmes has shown beneficial impacts on disease caused by related non-vaccine microorganisms. This knowledge has influenced the way new vaccines are designed, developed, and evaluated in real-life settings. Some of the new vaccines are now designed with the specific aim of having a greater breadth of protection. Ideal vaccine antigens therefore include epitopes with conserved homology across related pathogen types, because it is not always possible to include the antigens of all the individual types of a given pathogen species. The use of novel adjuvants with greater immunostimulatory properties can also contribute to improved overall vaccine cross-reactivity, as could the use of antigen delivery platforms. The growing body of evidence allows us to better understand the full impact of vaccines – beyond vaccine-type disease – which should be taken into consideration when assessing the full value of vaccination programmes.

Contents

* Corresponding author.
E-mail address: ivo.x.vojtek@gsk.com (I. Vojtek).

https://doi.org/10.1016/j.vaccine.2018.12.005
0264-410X/

1. Introduction

It is well known that vaccines can induce immune responses to antigens other than those contained in the vaccine, termed "cross-reactivity". This can apply to related species within the same genus (e.g. administration of cowpox to protect against smallpox; or *Mycobacterium bovis* in the Bacillus Calmette–Guérin [BCG] vaccine to protect against tuberculosis). This mechanism is also observed between serotypes/genotypes of the same pathogen species, e.g. cross-protection against human papillomavirus (HPV)-31/33/45 following administration of a vaccine containing HPV-16/18 [1].

"Cross-protection" implies clinically significant protection against infection/disease due to an immune response elicited against a related organism, i.e. when "cross-reactivity" results in a measurable clinical impact. The extent of cross-protection is sometimes assessed during vaccine trials. However, the sample size of clinical trials typically does not allow for individual estimates of cross-protection across a range of microorganism types because the prevalence of any single type is usually too low. Therefore, confirmatory evidence normally comes from post-licensure studies following the implementation of immunization programmes. Representative data (Table 1) – showing the additional protection provided by vaccines across a range of vaccine-preventable diseases – will be discussed in this expert review article, along with possible modes of action to complete the understanding of cross-reactivity as an inherent property of the human immune system. Finally, we will discuss ways to leverage and improve this beneficial effect. The scope of this article is limited to antigen-specific cross-reactivity and does not include heterologous effects of vaccines mediated by non-specific immunomodulation, such as the protective benefits of BCG and measles vaccinations on all-cause mortality [2].

2. Evidence of cross-reactivity/protection after vaccination

2.1. Vaccinia and mycobacteria

The observation that natural infection with cowpox provided protection against smallpox ultimately led to the development of

Table 1
Examples of cross-protection (i.e. protection against clinical infection/disease) and cross-reactivity (i.e. evidence of an immune response to related antigens) for various vaccines.

Disease target	Vaccine	Vaccine content	Cross-reactivity/protection against [refs]	Comments
Smallpox	Cowpox	Cowpox virus	Smallpox virus [3]	Deliberate cross-protection led to smallpox eradication
Tuberculosis (*M. tuberculosis*)	BCG	*M. bovis*	*M. leprae* (leprosy) [4]	Cross-protection against target (tuberculosis) and leprosy (clinical trial data)
IPD	PCV-7	4, 6B, 9V, 14, 18C, 19F, 23F	6A [7,10–13]	Cross-protection based on clinical trial and post-licensure data
	PHiD-CV	As PCV-7 plus 1, 5, 7F	6A [8,15]; 19A [8,14,15]	Cross-protection based on clinical trial data
	PPSV-23	As PHiD-CV plus 2, 3, 8, 9N, 10A, 11A, 12F, 15B, 17F, 19A, 20, 22F, 33F	6A, 6C, 6D [17]	Cross-reactivity based on serological study data
HPV-associated genital and anal lesions	*Cervarix*	HPV-16/18	High-risk HPV-31/33/45 [1,23]; low-risk HPV-6/11 [24]	Cross-protection based on clinical trial and post-licensure data
	Gardasil	HPV-6/11/16/18	High-risk HPV-31 [26,27]	Cross-protection based on clinical trial data
Rotavirus gastroenteritis	*Rotarix*	G1P[8]	G2P[4], G3P[8], G4P[8], G8P[4], G9P[8] [37,45]	Cross-protection based on clinical trial data
	RotaTeq	G1, G2, G3, G4, and P[8]	G8, G9, P[4], P[6] [37]	Cross-protection based on clinical trial data
Meningococcal meningitis	MenB-4C	MenB	MenC, MenW, MenX [54,55]; MenY [56]	Cross-reactivity based on serological study data
	MeNZB	MenB	*N. gonorrhoeae* [61,62]	Cross-protection based on post-licensure data
Seasonal influenza	Various adjuvanted trivalent vaccines	Two influenza A types and one influenza B type	Related strains [64,65,67]	Cross-reactivity based on serological study data
Pandemic H1N1 influenza	Trivalent vaccine	A/Brisbane/59/2007(H1N1)-like	Pandemic H1N1 influenza [68]	Possible cross-protection based on clinical trial data
Pandemic influenza H5N1	*Prepandrix*	A/H5N1/Vietnam/1194/2004 strain	A/H5N1/Indonesia/5/2005; A/H5N1/turkey/Turkey/1/2005; A/H5N1/Anhui/1/2005 [70,71]	Cross-reactivity based on serological study data
TBE	*Encepur*; *FSME-Immun*	TBEV-Eu	TBEV-Fe, TBEV-Sib [76]; OMFV [81], JEV [80], WNV [79]	Cross-reactivity based on serological study data
Rabies	PCECV	RABV	ABLV, EBLV, DUVV, BBLV, MOKV [83,84]	Cross-reactivity based on serological study data

ABLV: Australian bat lyssavirus; BBLV: Bokeloh bat lyssavirus; BCG: Bacillus Calmette–Guérin; DUVV: Duvenhage virus; EBLV: European bat lyssavirus; HPV: human papillomavirus: IPD: invasive pneumococcal disease; JEV: Japanese encephalitis virus; MenB: meningococcal serogroup B; MenB-4C: 4-component meningococcal serogroup B vaccine; MenC: meningococcal serogroup C; MenX: meningococcal serogroup X; MenY: meningococcal serogroup Y; MeNZB: meningococcal serogroup B outer membrane vesicles vaccine; MOKV: Mokola virus; OHFV: Omsk haemorrhagic fever virus; PCECV: purified chick embryo cell rabies vaccine; PCV-7: 7-valent pneumococcal conjugate vaccine; PHiD-CV: non-typeable *Haemophilus influenzae* protein D conjugate vaccine; PPSV-23: 23-valent pneumococcal polysaccharide vaccine; RABV: rabies virus; TBE: tick-borne encephalitis; TBEV: tick-borne encephalitis virus; TBEV-Eu: 'European' tick-borne encephalitis virus subtype; TBEV-Fe: 'Far-Eastern' tick-borne encephalitis virus subtype; TBEV-Sib: 'Siberian' tick-borne encephalitis virus subtype; WNV: West-Nile virus.

vaccination against smallpox [3] (Table 1). Early smallpox vaccines contained material from cowpox lesions – which may have contained more than one species of poxvirus – while newer smallpox vaccines contain purified vaccinia virus, thus relying entirely on cross-protection.

Another example of cross-protection is the BCG vaccine, which contains *M. bovis*, but protects against tuberculosis (caused by *M. tuberculosis*) (Table 1). Interestingly, this vaccine also provides protection against leprosy (caused by the much more distantly-related *M. leprae*). Although the level of protection varies widely by study (20–90%), a meta-analysis has found overall vaccine efficacy of BCG against leprosy of 55% [4].

2.2. Invasive pneumococcal disease

Although around 90 different *Streptococcus pneumoniae* serotypes have been identified [5], seven (4, 6B, 9V, 14, 18C, 19F, and 23F) caused the majority of invasive pneumococcal disease (IPD) in North America before the introduction of pneumococcal vaccines [6]. Initial vaccination strategies utilized a 7-valent pneumococcal conjugate vaccine (PCV-7) targeting these seven serotypes, while newer vaccines include antigens from more serotypes. These include a 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine (PHiD-CV, *Synflorix,* GSK, Belgium) and a 13-valent pneumococcal-diphtheria cross-reacting material 197 protein conjugate vaccine (PCV-13, *Prevenar 13*, Pfizer, USA). These contain antigens of the serotypes as shown in Table 2.

Case-control studies have reported vaccine effectiveness >75% for PCV-7, PHiD-CV, and PCV-13 against vaccine-serotype IPD [7–9]. Various trials of PCV-7 and PHiD-CV have shown evidence of cross-protection against some non-vaccine serotypes in PCV-13 (Table 2). For example, a US case–control study reported that PCV-7 was effective against IPD caused by serotype 6A [7] (Table 2). A decline in the incidence of IPD due to 6A has also been observed in subsequent surveillance studies in various countries following PCV-7 introduction [10–13]. However, PCV-7 has shown little/no efficacy against 19A in clinical trials [7,14] or surveillance studies [10–12]. A Brazilian case–control study has shown protection with PHiD-CV against IPD caused by 19A, but not 6A [8]. However, subsequent cohort studies from Quebec and Finland have reported PHiD-CV vaccine effectiveness against serotypes 19A [14] or 6A and 19A [15] IPD (Table 2). The inconsistencies in efficacy against 6A are likely due to the low numbers of 6A cases. Interestingly, the cross-protection of PHiD-CV against 19A IPD (62–82%; Table 2 [8,14,15]) is almost as high as the vaccine-serotype protection of PCV-13 against 19A IPD (~85%) [9].

The differences between the observed clinical impacts of PCV-7 and PHiD-CV on 19A IPD illustrate the importance of vaccine design on the protective immune response to closely related antigens. While both vaccines include the 19F antigen, there appears to be a qualitative difference in their immune response in terms of protection against 19A IPD (Table 2). One possible explanation is the different chemistry used to conjugate the polysaccharides to proteins. While PHiD-CV employs cyanylation-mediated conjugation of 19F to a diphtheria toxoid carrier protein, which supposedly preserves the 19F epitope [16], PCV-7 uses reductive amination to conjugate 19F to a cross-reacting material 197 carrier, which may affect the 19F epitopes by opening one of the saccharide rings. The cross-reactive antibodies to 19A induced with PCV-7 have lower opsonophagocytic activity and lower titres than the cross-reactive antibodies to 19A induced with PHiD-CV [16].

Besides the above-mentioned cross-protection of serotype 6B against 6A, the 6B serotype contained in a 23-valent pneumococcal polysaccharide vaccine has been reported to induce cross-functional immune responses against serotypes 6A, 6C, and 6D [17] (Table 1).

Table 2
Evidence of cross-protection with PCV-7 and PHiD-CV against non-vaccine-serotypes associated with IPD.

PCV-13 serotypes	Vaccine efficacy (95% CI) [ref]	
	PCV-7	PHiD-CV
1	–	Vaccine component
3	30 (−131 to 79) [7][a]	8 (−272 to 77) [8][a] −354 (−2006 to −26) [14][b] −289 (−2707 to 24) [15][b]
4	Vaccine component	Vaccine component
5	–	Vaccine component
6A	76 (39–90) [7][a]	15 (−312 to 82) [8][a] 100 (41–100) [15][b]
6B	Vaccine component	Vaccine component
7F	−22 (−444 to 73) [7][a] 15 (−161 to 72) [14][b]	Vaccine component
9V	Vaccine component	Vaccine component
14	Vaccine component	Vaccine component
18C	Vaccine component	Vaccine component
19A	26 (−45 to 62) [7][a] 42 (−9 to 69) [14][b]	82 (11–96) [8][a] 71 (24–89) [14][b] 62 (20–85) [15][b]
19F	Vaccine component	Vaccine component
23F	Vaccine component	Vaccine component

–, not reported; CI, confidence interval; IPD, invasive pneumococcal disease; PCV-7, seven-valent pneumococcal conjugate vaccine; PCV-13, 13-valent pneumococcal conjugate vaccine; PHiD-CV, 10-valent pneumococcal non-typeable *Haemophilus influenzae* protein D conjugate vaccine.
[a] Case–control studies.
[b] Cohort studies.

2.3. Human papilloma virus

Over 150 HPV types have been identified [18], but two (HPV-16 and HPV-18, both "high-risk" oncogenic types) account for approximately 70% of cervical cancer cases (in terms of oncogenesis), with HPV-31/33/35/45/52/58 accounting for most other cases [19]. Of the low-risk types, HPV-6/11 are most commonly associated with genital warts. Currently, three HPV vaccines are widely licensed: the AS04-HPV-16/18 vaccine, which is adjuvanted with 50 μg 3-O-desacyl-4'-monophosphoryl lipid A (MPL) adsorbed on aluminium salt (500 μg Al^{3+}) (AS04) (*Cervarix*, GSK, Belgium) and HPV-6/11/16/18 and HPV-6/11/16/18/31/33/45/52/58 vaccines, both with amorphous aluminium hydroxyphosphate sulphate adjuvants (*Gardasil* and *Gardasil 9*, Merck, USA).

A serological study of HPV-16/18 and HPV-6/11/16/18 showed that both vaccines elicited immune responses to non-vaccine HPV types (HPV-31/33/45/58) [20]. In a recent meta-analysis, AS04-HPV-16/18 and HPV-6/11/16/18 vaccines induced seropositivity to clinically important non-vaccine types, significantly more so for AS04-HPV-16/18 versus HPV-6/11/16/18 against HPV-31 and HPV-45 (Fig. 1A) [21].

In a large clinical trial, overall efficacy of AS04-adjuvanted HPV-16/18 vaccine against various cervical intraepithelial neoplasia (CIN) endpoints (due to any HPV type) in initially HPV-naïve women after 4 years were greater than the expected efficacy based on the proportions of HPV-16/18-associated cases in the control arm and that predicted from vaccine efficacy against HPV-16/18 alone (Fig. 1B) [22]. These increases in observed vaccine efficacy appear to be due to cross-protection [22]. Further examination of the data from this study showed that the AS04-HPV-16/18 vaccine provided significant cross-protection against 6-month persistent infection and CIN2+ (with or without HPV-16/18 infection) associated with five non-vaccine types for the HPV-naïve cohort; and with four non-vaccine types for the total vaccinated cohort (Table 3) [1]. These observations were recently confirmed in a

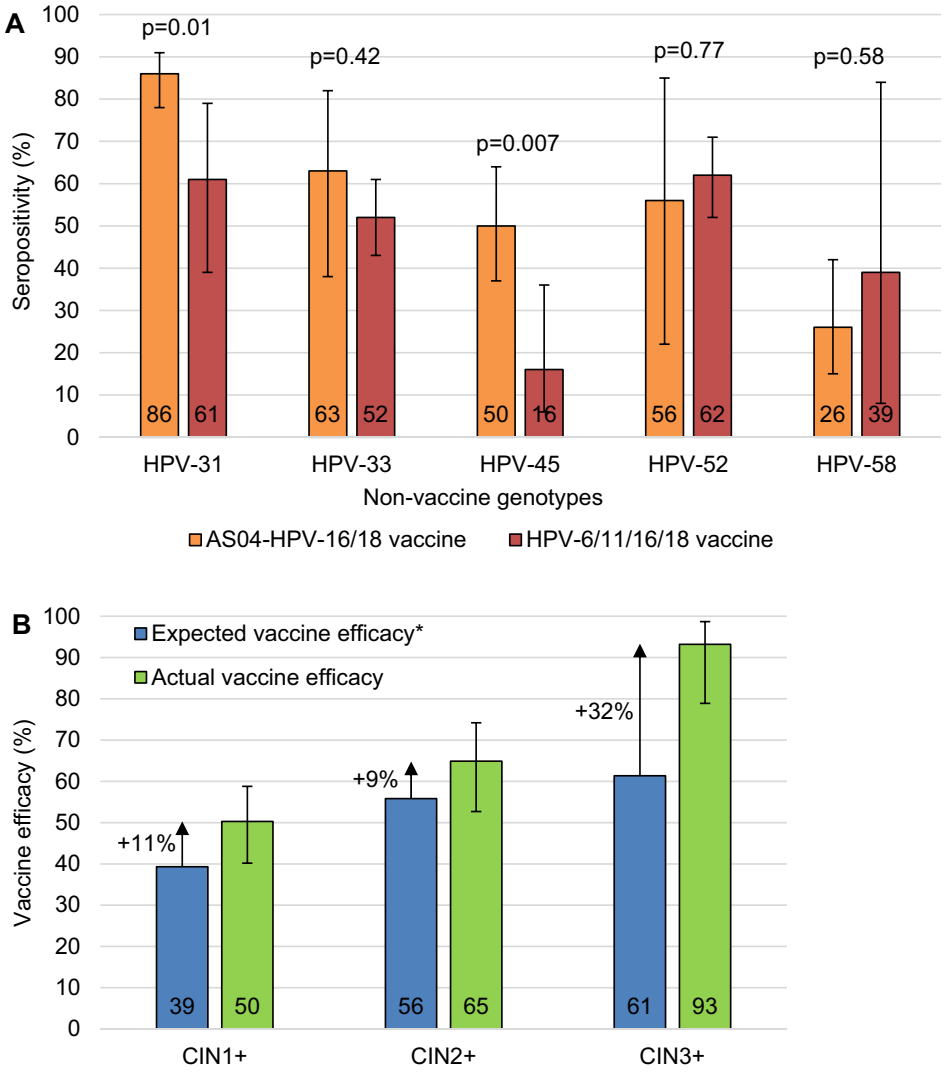

Fig. 1. Examples of cross-protection against non-vaccine HPV genotypes: (A) pooled estimates for seroconversion against non-vaccine genotypes for the AS04-HPV-16/18 and HPV-6/11/16/18 vaccines (p values show the significance of the difference in vaccine effectiveness) [21] and (B) expected* and actual overall vaccine efficacies of the AS04-HPV-16/18 vaccine against various endpoints among women who were HPV-naïve at baseline [22]. The additional efficacy is due to cross-protection against other HPV genotypes. *Expected VE was calculated as (control cases associated with HPV-16/18)/(all control cases) × (VE for HPV-16/18). CIN, cervical intraepithelial neoplasia.

Table 3
Summary of cross-protective vaccine efficacies against high-risk HPV types for the AS04-HPV-16/18 and HPV-6/11/16/18 vaccines.

	HPV-31	HPV-33	HPV-35	HPV-39	HPV-45	HPV-51	HPV-52	HPV-56	HPV-58	HPV-59	HPV-66	HPV-68
AS04-HPV-16/18vaccine [1]												
HPV-naïve cohort												
6-month persistent infection	77.1	43.1	×	?	79.0	25.5	18.9	×	×	×	×	?
CIN2+ (± HPV-16/18)	89.4	82.3	?	?	100	70.2	?	100	?	?	?	?
CIN2+ (no HPV-16/18)	83.4	76.3	?	?	?	×	×	?	×	?	?	×
TVC												
6-month persistent infection	46.3	26.3	×	×	54.5	13.7	×	×	×	×	×	×
CIN2+ (± HPV-16/18)	47.0	51.5	?	?	90.5	50.0	×	?	?	?	?	?
CIN2+ (no HPV-16/18)	?	50.0	?	?	?	?	×	×	×	×	×	×
HPV-6/11/16/18 vaccine												
HPV-naïve cohort [26]												
Infection	46.2	?	?	NR	?	NR	?	NR	×	?	NR	NR
CIN1-3/AIS	56.9	?	?	?	×	×	?	?	?	?	NR	NR
CIN2-3/AIS	70.0	?	×	?	×	×	?	?	?	?	NR	NR
ITT cohort [27]												
≥6-month PI	33.6	?	×	NR	?	NR	×	NR	?	24.6	NR	NR
CIN1-3/AIS	26.0	?	?	×	?	×	?	?	28.1	37.6	NR	NR

All listed values, which represent vaccine efficacies (%), have positive lower 95% CIs; ? indicates positive vaccine efficacy but negative lower 95% CI; ×, minimal (<10%) or negative vaccine efficacy; NR, not reported.
± HPV-16/18, with or without co-infection with HPV-16/18; AIS, adenocarcinoma in situ; CIN, cervical intraepithelial neoplasia; HPV, human papillomavirus; ITT, intention-to-treat; no HPV-16/18, excluding co-infection with HPV-16/18; TVC, total vaccinated cohort.

cross-sectional study conducted in Scotland 7 years after the introduction of an AS04-HPV-16/18 vaccination programme [23]. The prevalence of vaccine-type HPV was reduced by 89.1% (95% confidence interval [CI] 85.1–92.3%), but there were also reductions of comparable magnitudes in non-vaccine types: HPV-31, 93.8% (95% CI 83.8–98.5%); HPV-33, 79.1% (95% CI 64.2–89.0%); and HPV-45, 82.6% (95% CI 61.5–93.9%) [23].

The AS04-HPV-16/18 vaccine has also been found to provide moderate cross-protection against persistent infection with low-risk non-vaccine genotypes associated with genital warts, with vaccine efficacies against 6-month persistent infection against HPV-6/11 of 34.5% (95% CI 11.3–51.8%) and against HPV-74 of 49.5% (95% CI 21.0–68.3%) [24]. Furthermore, ecological data from England suggest that vaccination with the AS04-HPV-16/18 vaccine has resulted in up to a 50% reduction in the incidence of genital warts [25].

Studies of the HPV-6/11/16/18 vaccine have also demonstrated reductions in HPV infection due to non-vaccine types. As shown in Table 3, the HPV-6/11/16/18 vaccine provided cross-protection against HPV-31 in the HPV-naïve cohort [26]; with additional low levels of cross-protection against HPV-58/59 in the intention-to-treat cohort [27]. Post-licensure data also indicate significant cross-protection against HPV-31, but not for the other types [28]. This seemingly lower cross-protection with the HPV-6/11/16/18 vaccine versus the AS04-HPV-16/18 vaccine has been attributed to their different adjuvants [29,30]. The AS04-HPV-16/18 vaccine contains AS04, which enhances the immune response by triggering a local cytokine response [31], while the HPV-6/11/16/18 vaccine contains amorphous aluminium hydroxyphosphate sulphate.

2.4. Rotavirus

Based on VP6 genetic variability and serological reactivity, rotaviruses are classified into eight groups (A–H) [32]. These are further classified into glycoprotein (G) and protease-sensitive (P) serotypes/genotypes on the basis of their genomic sequence and the serological characteristics of their outer capsid proteins, VP7

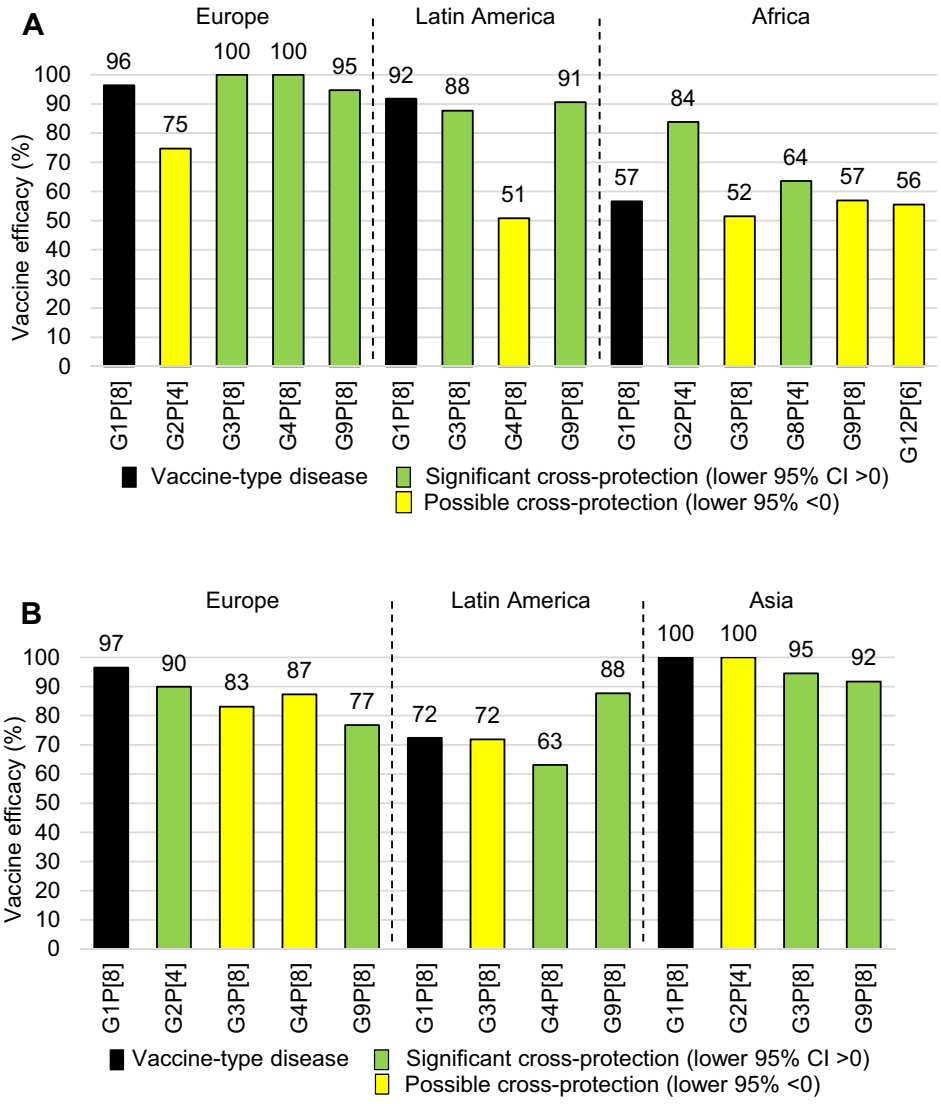

Fig. 2. Efficacy of monovalent rotavirus vaccine against vaccine-type and non-vaccine type severe* rotavirus gastroenteritis during (A) the first year of life in Europe, Latin America, and Africa; and (B) the second year of life in Europe and Latin America or the first 2 years of life in Asia [45]. *Score ≥ 11 on the Vesikari scale [46] for Europe, Africa, and Asia; an episode of diarrhoea with or without vomiting that required hospitalization and/or re-hydration therapy in a medical facility for Latin America. European populations: first year: vaccine n = 2572; placebo n = 1302; second year: vaccine n = 2554; placebo n = 1294. Latin American populations: first year: vaccine n = 9009; placebo n = 8858; second year: vaccine n = 7175; placebo n = 7062. African populations: first year: vaccine n = 2974; placebo n = 1443. Asian populations: first 2 years: vaccine n = 5263; placebo n = 5256.

and VP4, respectively [33]. A range of genotypes may be characterized on the basis of G-P combinations, with G1P[8], G2P[4], G3P[8], G4P[8], and G9P[8] being the most common in the pre-rotavirus vaccine era [34]. In contrast to the important variability observed among G-and P-types, little diversity is found among VP6 subgroups and nonstructural protein 4 genotypes circulating in humans [35]. Although the role of these proteins in cross-reactivity has not been fully elucidated, the best evidence of heterologous protection arises from empirical observations of natural rotavirus infections [35].

Indeed, rotavirus vaccines were specifically designed to mimic the cross-serotype immunity that occurs following natural infection with a rotavirus [36]. Currently, two vaccines are widely available: a monovalent oral live attenuated human rotavirus vaccine containing the G1P[8] strain (*Rotarix*, GSK, Belgium) and a pentavalent human-bovine reassortant vaccine containing G1, G2, G3, G4, and P[8] strains (*RotaTeq*, Merck, USA) [37]. Despite clear differences in vaccine valency, data suggest that both vaccines have similar effectiveness against rotavirus gastroenteritis (RVGE) [37,38]. This implies broad immunological cross-reactivity and clinical protection against disease induced by non-vaccine serotypes.

Further evidence for cross-protection with the monovalent rotavirus vaccine has been obtained from studies conducted across Latin America, Africa, Europe, and Asia [39–44], which showed substantial efficacy against RVGE due to the vaccine type (G1 [P8]) and against disease due to a range of other strains (Fig. 2) [45,46]. In a pooled analysis, the monovalent vaccine was found to have, in high–middle income countries, a 77% (95% CI 58–86%) effectiveness against the G1P[8] vaccine strain, 72% (95% CI 49–84%) against partially heterotypic strains (G3P[8], G4P[8], G9P [8]), and 67% (95% CI 52–77%) against a fully heterotypic strain (G2P[4]) [37]. Using the same criteria, the pentavalent vaccine was found to have 76% (95% CI 64–89%) effectiveness against its vaccine types (single human rotavirus VP7 or VP4 antigen) and 81% (95% CI 43–93%) effectiveness against non-vaccine types (single human rotavirus VP7 or VP4 antigen not included in the pentavalent vaccine) [37]. These results were confirmed in a more recent meta-analysis where both vaccines provided good protection against RVGE, with non-significantly higher odds ratios for effectiveness for the monovalent vaccine (e.g. 2.23, 95% credible interval 0.72–5.20 against severe disease up to 2 years) [38], highlighting the importance of cross-protection with these two rotavirus vaccines even if they are based on different approaches.

2.5. Meningococcal meningitis

There are 13 serogroups of Neisseria meningitidis, but most invasive human disease is due to serogroups A, B, C, W-135, X and Y [47]. A number of monovalent and polyvalent vaccines directed against the capsular polysaccharides (CPS) of meningococcal groups A, C, W-135, and Y have been licensed and are widely used [48]. However, development of a vaccine against meningococcal serogroup B (MenB) CPS had been hindered by potential molecular similarity to a human poly-sialyted neuronal cell adhesion molecule, which reduces immunogenicity in humans and raises concerns regarding the potential induction of autoimmune disease [49].

Initially, vaccines against MenB outer membrane vesicles (OMVs) were developed, selecting the MenB porin A as the vaccine antigen. However, antigenic diversity and immunodominance of certain porin A antigens resulted in monovalent MenB vaccines with limited cross-reactivity. While effective in controlling the strain-specific outbreaks for which they were developed, they cannot provide the necessary broader protective activity against the diverse range of MenB strains in global circulation [50].

To find alternative antigenic targets, MenB surface antigens with high immunogenicity, including the factor H binding protein (fHbp), neisseria adhesin A (NadA), and neisseria heparin binding antigen (NHBA) were identified by reverse vaccinology [47]. Using this approach, MenB-4C (*Bexsero*, GSK, Belgium), a four-component vaccine combining fHbp, NadA, and NHBA antigens and an OMV antigen derived from a MenB strain associated with an outbreak in New Zealand, has been developed and is widely available [49]. Another vaccine, MenB-FHbp (*Trumenba*, Pfizer, USA), a bivalent vaccine containing two antigenically distinct fHbp variants is also available in the US and Europe [51].

The proportion of circulating MenB strains in different geographical populations that will likely be covered by MenB-4C has been estimated – using the Meningococcal Antigen Typing System (MATS) – to be 66–91% globally [52]. However, it is likely that MATS underestimates MenB strain coverage because it does not include the potential for cross-protection [53].

Inclusion of the sub-capsular antigens (fHbp, NHBA, and NadA) in MenB-4C has the potential to confer protection against other meningitis serogroups with common epitopes [47]. Studies using either MATS data with predicted human serum bactericidal antibody (hSBA) responses to meningitis serogroups (C, W, and Y) or directly measuring hSBA responses using sera from subjects immunized with MenB-4C vaccine support this assumption (Table 1). In an Australian study, which used MATS data to predict MenB coverage with MenB-4C (76% predicted coverage), 108 non-MenB serogroup isolates were also tested [54]. Of these, 56% exceeded immune correlates of protection thresholds for at least one of the antigens included in MenB-4C: MenC (64%); MenW-135 (63%); and MenY (37%) [54]. A study evaluating 147 non-MenB isolates from Europe and Brazil, which measured hSBA responses using sera from subjects immunized with MenB-4C vaccine, reported responses against MenC, MenW, and MenY ranging from 45% to 90% [55]. Another study, using hSBA assays with pooled sera from vaccinated subjects, reported that MenB-4C might provide coverage against nine MenX isolates from Africa (but not two unrelated MenX isolates from France) [56]. More recently, analysis of MenW isolates from the UK has shown high hSBA titres ($\geq$1:32) against all six strains in which MATS data predicted coverage following immunization with MenB-4C [57]. These preliminary data suggest that additional protection against non-MenB serogroups may be provided by the MenB-4C vaccine. Indeed, in the UK, the Joint Committee on Vaccination and Immunisation has recognized that the MenB-4C vaccine is likely to provide some protection against other meningitis serogroups, including MenC [58].

For the MenB-FHbp vaccine, an alternative system, the Meningococcal Antigen Surface Expression (MEASURE) assay, which quantifies the fHBP cell surface concentration, is used. MenB-FHbp has also been predicted to elicit responses to diverse MenB strains [32,35], although there is, as yet, limited clinical data with this vaccine.

Lastly, there is substantial (80–90%) genetic homology between *Neisseria* species, including *N. meningitidis* and *N. gonorrhoeae* [59]. Meningitis vaccines may therefore provide some clinical protection against gonorrhoea, for which there is currently no specific effective vaccine [60]. Retrospective data from Norway suggest that there may be some decline in gonorrhoea incidence among MenB OMV vaccine recipients [61] (Table 1). A recent retrospective case–control study in New Zealand has specifically evaluated the effect of a specific MenB OMV vaccine (MeNZB) on gonorrhoea [62]. Subjects who received a complete MeNZB vaccination schedule were found to be significantly less likely to have gonorrhoea than those who did not ($p < 0.0001$), with an estimated vaccine effectiveness of 31% (95% CI 21–39%) [62].

2.6. Influenza

Human influenza viruses are classified into three types (A, B, and C) [63]. Influenza A viruses are divided into multiple subtypes based on surface haemagglutinin (H) and neuraminidase (N) proteins (e.g. H1N1, H3N2, H5N1, H7N9). These are further subdivided into clades, which usually have different antigenic characteristics and are identified by numbers or by representative strains (e.g. A/Michigan/45/2015-like H1N1). Influenza B viruses are divided into two antigenically distinct lineages (B/Victoria and B/Yamagata), and further by clades classically identified by representative strains (e.g. B/Brisbane/60/2008-like for one of the B/Victoria clade).

As reviewed by various authors [64–66], immunogenicity studies have shown that influenza vaccines against H1N1, H3N2, and B influenza viruses can induce seroprotection against related strains (e.g. a vaccine containing the seasonal A/H1N1/Beijing/262/95 virus can induce seroprotection against the new pandemic A/H1N1/New Caledonia/20/99 virus [67]) (Table 1). The extent of seroprotection against related strains compared to vaccine strains varies widely. It is known that this is linked to how much the vaccine strains "match" the features of the circulating strains each season [64,65]. A placebo-controlled study has reported potential cross-protection of a non-adjuvanted intramuscularly administered seasonal influenza vaccine (containing A/Brisbane/59/2007 (H1N1)-like) against pandemic H1N1 influenza [68] (Table 1). This was significant when assessed by serology (0.09 vs 0.17 cases per person-year; vaccine efficacy 47%; p = 0.01), but not by reverse-transcription polymerase chain reaction (0.02 vs 0.02 cases per person-year; vaccine efficacy −32%; p = 0.61) [68].

In addition, some studies showed an enhanced cross-protection with intradermally administered vaccines and intramuscularly administered microfluidized emulsion (MF59)-adjuvanted vaccines compared to conventional intramuscular administration of unadjuvanted vaccines [64]. These studies suggest that adjuvanted seasonal influenza vaccines can provide some extra protection against related strains that are not included in the vaccine. This is important as it potentially broadens the vaccine effectiveness in this disease that is caused by antigenically unstable viruses. As reviewed by Chada et al. [69], various studies have shown that vaccines adjuvanted with MF59 or AS03 (an adjuvant system containing α-tocopherol and squalene in an oil-in-water emulsion) against pathogenic avian H5N1 can induce broad cross-clade immunity to antigenically diverse strains. For example, vaccination with an AS03-adjuvanted A/H5N1/Vietnam/1194/2004 (clade 1) vaccine resulted in cross-clade immunity against A/H5N1/Indonesia/5/2005 (clade 2.1), A/H5N1/turkey/Turkey/1/2005 (clade 2.2), and A/H5N1/Anhui/1/2005 (clade 2.3) (seroconversion rates 75–85%) despite significant antigenic variability between these clades [70,71] (Table 1). Interestingly, a non-adjuvanted version of this vaccine did not elicit cross-reactivity [70,71]. Cross-reactivity has also been reported following immunization with adjuvanted pandemic H1N1 vaccines [72,73]. Overall, these findings have welcome implications regarding vaccine stockpiling when preparing for future influenza pandemics [69].

2.7. Flaviviridae

The *Flaviviridae* family includes various arthropod-borne viruses, e.g. Yellow fever virus, dengue virus, Zika virus, West Nile virus, Japanese encephalitis virus, and tick-borne encephalitis (TBE) virus (TBEV). These can cause a wide range of diseases including haemorrhagic fever, hepatitis, and encephalitis. While these viruses differ in their natural history and pathogenicity profiles, they have the envelope glycoprotein – which governs membrane fusion – as a common structure [74].

Intra-species cross-reactivity between distinct subtypes is well illustrated in the experience seen with immunization against TBE. TBEVs are subdivided into three main types: TBEV-Eu (a European subtype); TBEV-Fe (a Far-Eastern subtype); and TBEV-Sib (a Siberian subtype) [75]. Available vaccines are based on inactivated whole TBEV. In Europe, two licensed vaccines directed against TBEV-Eu are available: *Encepur* (GSK, Belgium) and *FSME-Immun* (Baxter, Austria) [75]. In Russia, two vaccines against TBEV-Fe are available: *TBE Moscow* (Chumakov Institute of poliomyelitis and Viral encephalitides) and *EnceVir* (Microgen, Tomsk) [75]. As shown in a recent review of 14 serological studies, both European vaccines induce strong, persistent antibody responses to a wide variety of TBEV types, with very high seroconversion/seropositivity rates (Table 4) [76]. Another review has discussed evidence suggesting cross-protective capabilities of vaccines against different Japanese encephalitis serocomplex viruses [77].

As recently reviewed by Priyamvada et al. [78], there is also evidence of interspecies cross-reactivity between dengue virus and Zika virus. Immunization with a vaccine against a specific flavivirus has also been found to be accompanied by some degree of

Table 4
Immunogenicity against heterologous subtypes after two or three doses of TBEV-Eu vaccines, based on 14 studies as reviewed by Domnich et al. [76].

	Sero-outcome[a] (%)			
	Encepur		FSME-Immun	
	Two doses	Three doses	Two doses	Three doses
TBEV-Fe strains				
139	63	99	79–100	–
205	4–72	79–100	72–100	75–97
KH98–5	–	–	100	–
Oshima 5–10	–	–	88	100
P-69	27–71	64–100	–	–
P-73	57–94	95–100	–	78–88
P-202	52–92	98–100	–	–
Sofjin	–	100	100	100
VL99-m11	–	–	100	–
TBEV-Sib strains				
IR99-2f7	–	–	100	–
Kolarovo-2008	–	100	–	–
Vasilchenko	–	–	–	100

TBEV-Eu: European tick-borne encephalitis virus subtype; TBEV-Fe: Far-Eastern tick-borne encephalitis virus subtype; TBEV-Sib: Siberian tick-borne encephalitis virus subtype.

[a] Percentages of seropositive or seroconverted (depending on the study) subjects at 0.5–12 months after the second dose and 0.75–84 months after the third dose by a range of assays (neutralization test, enzyme-linked immunosorbent assay for immunoglobulin G, haemagglutination inhibition, and indirect immunofluorescence assay).

immunological cross-reactivity against other flaviviridae [79–81]. For example, a TBEV vaccine has been reported to provide full protection against Omsk haemorrhagic fever virus infection in mice [81]. Further, prior TBEV vaccination has been reported to enhance initial immune responses to Japanese encephalitis virus immunization in humans [80], and may also induce neutralizing antibodies against West Nile virus [79]. However, it is not always clear to what extent cross-reactivity results in cross-protection.

2.8. Rabies

Rabies is caused by the rabies virus and other phylogenetically related viruses, all from the genus *Lyssavirus* [82]. Various human rabies virus vaccines are available, [82,83]. Human diploid cell and purified chick embryo cell rabies vaccines in particular, have been shown to elicit cross-reactive neutralizing antibodies against Australian bat lyssavirus and European bat lyssavirus [83,84] (Table 1). The purified chick embryo cell vaccine has additionally shown cross-reactivity against Duvenhage virus and Bokeloh bat lyssavirus [83].

3. Biological rationale for cross-reactivity

In vaccination, the principal aim is to elicit strong immune responses (mainly antibody responses) to an antigen or antigens, which are typically accessible, surface-exposed immunogenic structures of the target pathogen. Often, these are involved in bacterial virulence or persistence. For instance, bacterial targets could include CPS [48] or OMVs in the case of meningitis vaccines [50]. Virus targets often include surface glycoproteins such as haemagglutinin and neuraminidase proteins in influenza vaccines [85]. Although antigens usually differ between serotypes/genotypes in terms of their immunogenic and structural properties, they may retain common – and sometimes significantly conserved – features such as shared epitopes, usually a feature of phylogenetically closely related members of a pathogen species. Conservation is also seen across more phylogenetically distant variants of the same species and even between species, as illustrated with the examples of smallpox and BCG vaccine previously mentioned. Consequently, vaccination using specific antigen targets can induce immune responses towards additional pathogen strains (and sometimes even different species). This forms the basis of cross- protection in vaccination, in which clinical protection beyond the target antigen(s) is observed.

3.1. Cross-reactivity as an intrinsic feature of the adaptive immune response

Besides the antigenic similarity described above, the phenomenon of cross-reactivity is also a consequence of the flexibility of interactions between T- and B-cell receptors and antigens, which rather than "one-to-one" resemble "several-to-several" and the resulting polyclonal adaptive response. In the cascade of the adaptive immune response, an epitope (also called antigenic determinant, which is the structure recognized by the immune system) is presented to naïve B cells and recognized with various levels of affinity. This triggers a selective process, resulting in selection and proliferation of B cells capable of producing antibodies that bind to this epitope in a process called affinity maturation. Binding of an antigen to a B cell represents one of the stimuli required for their proliferation. Another is the presence of T-helper cells, which are essential for the development of a strong and lasting immune response [86,87]. A single antigen typically contains various different epitopes, which can be recognized by multiple different clones of B cells. This leads to proliferation of all the different clones and is known as a polyclonal response [86,88]. An immune response to an antigen therefore classically raises many different antibodies to the various exposed epitopes on the antigen. There are several factors that support the wider range of B-cell specificity to antigens, one of which is the stimulation of the immune system early in the affinity maturation [88].

Specific antigenic determinants induce immune responses with antibodies recognizing and interacting with epitopes via complementary determinants (paratopes) in an area within the antibody variable region [88]. Such antigen–antibody interactions are mediated by their respective binding site (i.e. epitope–paratope) interactions, which range in respect to their strength, or affinity. This interaction is primarily a function of the level of epitope/paratope steric complementarity and ionic charge rather than amino acid sequence. As each paratope may interact with several different epitopes, both high- and low-affinity antibodies are produced following exposure of the immune system to an antigen. Some of these have high specificity to a small number of epitopes, while others have low specificity to a wider range of epitopes. This polyclonal response is one of the main underlying principles of cross-reactivity.

There is also a level of cross-reactivity in the T cells. Initially, it was thought that individual lymphocytes specifically recognized a single epitope of an antigen, with recognition of other antigens unlikely. More recent understanding of the immune system has questioned this concept. It has been proposed that the ability of a T-cell receptor to recognize more antigens is an evolutionary necessity. Following the one-pathogen-one-clonotype concept, recognition of $>10^{15}$ potential foreign peptides, which is necessary for effective immunity, would require 10^{15} T cells, which would weigh >500 kg [89,90]. The reliance of the immune system purely on monospecific T-cell receptors is therefore biologically implausible. There are about 10^{12} T cells in a human and $<10^{8}$ distinct T-cell receptors in the human naïve T-cell pool [90,91]. The capability of T-cell receptors to recognize different antigens is a biological need and cross-reactivity is one way that they may be able to do this [90]. Various mechanisms have been suggested to explain how T-cell receptor cross-reactivity may allow the limited T-cell pool to recognize a myriad of potential antigens: (1) induced fit; (2) differential T-cell receptor docking; (3) structural degeneracy; (4) molecular mimicry; and (5) antigen-dependent tuning of peptide-major histocompatibility complex flexibility [92].

4. Rational vaccine design incorporating cross-reactivity

The data discussed in this review clearly show that many vaccine antigens can elicit cross-reactive and cross-protective immune responses. With this in mind, new vaccines can be designed by carefully selecting antigens that are conserved between pathogen types in order to elicit the broadest response and, hence, provide the widest protection. Antigens that result in the generation of antibodies against a wide variety of naturally occurring antigens can then be used preferentially.

As one example, the 19F antigen that is included in PHiD-CV was subsequently found to provide protection against 19A IPD, presumably due to the very similar structures of these two serotypes [93]. Although this cross-protection developed by chance rather than by design, this knowledge has led to the search for conserved antigens, e.g. when designing MenB vaccines [47].

The content of seasonal influenza vaccines may vary each year, based largely on the epidemiological trends of the various circulating strains and clades but also on their antigenic characteristics. However, despite some cross-reactivity (especially with adjuvanted vaccines) [64–66], seasonal influenza vaccines offer only low levels of protection against seasonal influenza, or against

pandemic influenza. Therefore, the search for a "universal" influenza vaccine is underway. Approaches include eliciting a broader immune response that can confer protection against current seasonal influenza strains, or even targeting a protein or protein region that is conserved amongst both seasonal and pre-pandemic strains [94]. The latter approach could result in the ultimate cross-protective influenza vaccine.

5. Ways to improve cross-reactivity

As the adaptive immune system recognizes a pathogen by its antigens, the quality and quantity of the adaptive immune response are determined by the way these antigens are presented. With the move from whole pathogen to subunit and recombinant vaccines, vaccine antigens are expected to elicit a more specific – but less broad and less immunogenic – response [95]. Although this results in improved reproducibility and safety, it can also result in responses that are not sufficient to subsequently provide protection against the actual pathogen. As reviewed by various authors [96–99], adjuvants can be used to improve the immune response to the target antigens. Adjuvants also have the benefit of potentially improving cross-reactivity.

Adjuvants provide an early stimulus in clonal expansion, by activating antigen-presenting cells, which can further contribute to a broader polyclonal response. This enhancement of the immune response by adjuvants is well-documented in the example of influenza vaccines already described. MF59 has been used in adjuvanted influenza vaccines for many years, inducing greater responses to heterotypic strains, compared with unadjuvanted vaccines [64]. Similarly, as mentioned previously, an AS03-adjuvanted recombinant clade 1 H5N1 pre-pandemic vaccine has been shown to elicit a broad clade 2 cross-reactive immunity, while the antigen alone did not induce cross-reactive antibodies [70,71]. Also as previously mentioned, the AS04-HPV-16/18 vaccine appears to offer broader and stronger cross-protection than HPV-6/11/16/18 [1,21,26,27], likely due to its specialized adjuvant system [29,30].

How the various different adjuvants are able to activate innate cells and mechanisms, and how this translates into enhanced and modulated adaptive immune responses – particularly cross-reactiv ity/cross-protection – has not yet been fully elucidated. What is clear is that, by selecting and combining the most appropriate adjuvant components for a specific antigen, it is possible to design and formulate vaccines that deliver greater and broader protection (i.e. cross-protection) than existing vaccines [96].

Antigen-delivery platforms may also enhance the immune response – by delivering the vaccine antigens to the right compartments for optimal expression and processing – and hence potentially enhance polyclonal responses and broaden the range of protective immunity. For example, immunization with adenovirus-vectored centralized consensus hemagglutinin vaccine candidates (Adenovirus 4 and Adenovirus 5 vectors expressing H1, H3, and H5 consensus genes) has resulted in protection against challenge with lethal doses of heterologous influenza viruses in mice [100].

6. Conclusions

Many vaccines have been designed to target the most prevalent and/or most virulent strains of a pathogen. However, it is now clear – from serological studies, clinical trials, and post-licensure data – that many vaccines can elicit cross-reactive immune responses that may have an important additional clinical impact (i.e. cross-protection) on disease caused by non-vaccine strains or variants of the same pathogen. Of course, in addition to providing protection against infection/disease, cross-protection is also likely to have beneficial impacts on carriage and circulation, thereby providing some indirect (herd) protection. The observed effect of cross-reactivity is based on the intrinsic properties of the human adaptive immune system, namely the polyclonal nature of the humoral response and the capability of T- and B-cell receptors to recognize a variety of similar antigens. The evidence of vaccine effectiveness beyond that predicted solely by their antigen content has changed our understanding of the full impact – and cost-effectiveness – of immunization programmes with some vaccines. In several instances, the impact of immunization as we know it would not be the same without cross-reactivity, and this should therefore be taken into consideration when implementing new regimens. However, the cross-protective effects of each individual vaccine must be ascertained, as this can vary depending on factors such as epitope conservation and adjuvants. For vaccines against pathogens with important antigenic variability (e.g. pandemic influenza), cross-reactivity is actually an essential part of the vaccine design strategy to ensure optimal effectiveness. With the advent of the next generation of vaccine technologies (e.g. synthetic peptide antigens), cross-reactivity might become the solution to creating vaccines against highly antigenically and genetically diverse pathogens (e.g. rhinovirus or norovirus).

Acknowledgements

The authors would like to thank Alberta Di Pasquale for her valuable comments on the manuscript drafts. Business & Decision Life Sciences platform provided editorial assistance and publications coordination, on behalf of GSK. Vincent Laporte coordinated presentation development and editorial support, and Iain O'Neill and Jenny Lloyd (Compass Medical Communications Ltd. on behalf of GSK) provided scientific writing support.

Disclosure of interest

IV, PB, MD and BH are employees of the GSK group of companies and report ownership of stock options and/or restricted shares in the GSK group of companies.

Trademarks

Synflorix, *Bexsero*, *Rotarix*, *Prepandrix*, *Cervarix*, and *Encepur* are trademarks owned by, or licensed to, the GSK group of companies. *Prevenar 13* and *Trumenba* – Pfizer, USA; *Gardasil, Gardasil 9*, and *RotaTeq* – Merck, USA; *FSME-Immun* – Baxter, Austria; *TBE Moscow* – Chumakov Institute of poliomyelitis and Viral encephalitides; *EnceVir* – Microgen, Tomsk.

Funding

All costs associated with the development and publication of this manuscript were funded by GlaxoSmithKline Biologicals SA.

References

[1] Wheeler CM, Castellsague X, Garland SM, Szarewski A, Paavonen J, Naud P, et al. Cross-protective efficacy of HPV-16/18 AS04-adjuvanted vaccine against cervical infection and precancer caused by non-vaccine oncogenic HPV types: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. Lancet Oncol 2012;13:100–10.
[2] Higgins JP, Soares-Weiser K, Lopez-Lopez JA, Kakourou A, Chaplin K, Christensen H, et al. Association of BCG, DTP, and measles containing vaccines with childhood mortality: systematic review. BMJ 2016;355:i5170.
[3] Morabia A. Edward Jenner's 1798 report of challenge experiments demonstrating the protective effects of cowpox against smallpox. J R Soc Med 2018;111:255–7.

[4] Merle CS, Cunha SS, Rodrigues LC. BCG vaccination and leprosy protection: review of current evidence and status of BCG in leprosy control. Expert Rev Vaccines 2010;9:209–22.
[5] World Health Organization (WHO). Pneumococcal Disease. <http://www.who.int/biologicals/vaccines/pneumococcal/en/> [accessed on 20 June 2018].
[6] Johnson HL, Deloria-Knoll M, Levine OS, Stoszek SK, Freimanis Hance L, Reithinger R, et al. Systematic evaluation of serotypes causing invasive pneumococcal disease among children under five: the pneumococcal global serotype project. PLoS Med 2010;7.
[7] Whitney CG, Pilishvili T, Farley MM, Schaffner W, Craig AS, Lynfield R, et al. Effectiveness of seven-valent pneumococcal conjugate vaccine against invasive pneumococcal disease: a matched case-control study. Lancet 2006;368:1495–502.
[8] Domingues CM, Verani JR, Montenegro Renoiner EI, de Cunto Brandileone MC, Flannery B, de Oliveira LH, et al. Effectiveness of ten-valent pneumococcal conjugate vaccine against invasive pneumococcal disease in Brazil: a matched case-control study. Lancet Respir Med 2014;2:464–71.
[9] Dominguez A, Ciruela P, Hernandez S, Garcia-Garcia JJ, Soldevila N, Izquierdo C, et al. Effectiveness of the 13-valent pneumococcal conjugate vaccine in preventing invasive pneumococcal disease in children aged 7–59 months. A matched case-control study. PLoS One 2017;12:e0183191.
[10] Hanquet G, Lernout T, Vergison A, Verhaegen J, Kissling E, Tuerlinckx D, et al. Impact of conjugate 7-valent vaccination in Belgium: addressing methodological challenges. Vaccine 2011;29:2856–64.
[11] Harboe ZB, Valentiner-Branth P, Benfield TL, Christensen JJ, Andersen PH, Howitz M, et al. Early effectiveness of heptavalent conjugate pneumococcal vaccination on invasive pneumococcal disease after the introduction in the Danish Childhood Immunization Programme. Vaccine 2010;28:2642–7.
[12] Vestrheim DF, Hoiby EA, Bergsaker MR, Ronning K, Aaberge IS, Caugant DA. Indirect effect of conjugate pneumococcal vaccination in a 2+1 dose schedule. Vaccine 2010;28:2214–21.
[13] Park IH, Moore MR, Treanor JJ, Pelton SI, Pilishvili T, Beall B, et al. Differential effects of pneumococcal vaccines against serotypes 6A and 6C. J Infect Dis 2008;198:1818–22.
[14] Deceuninck G, De Serres G, Boulianne N, Lefebvre B, De Wals P. Effectiveness of three pneumococcal conjugate vaccines to prevent invasive pneumococcal disease in Quebec, Canada. Vaccine 2015;33:2684–9.
[15] Jokinen J, Rinta-Kokko H, Siira L, Palmu AA, Virtanen MJ, Nohynek H, et al. Impact of ten-valent pneumococcal conjugate vaccination on invasive pneumococcal disease in Finnish children–a population-based study. PLoS One 2015;10:e0120290.
[16] Poolman J, Frasch C, Nurkka A, Kayhty H, Biemans R, Schuerman L. Impact of the conjugation method on the immunogenicity of Streptococcus pneumoniae serotype 19F polysaccharide in conjugate vaccines. Clin Vaccine Immunol 2011;18:327–36.
[17] Kim HW, Lee S, Kim KH. Serotype 6B from a pneumococcal polysaccharide vaccine induces cross-functional antibody responses in adults to serotypes 6A, 6C, and 6D. Medicine (Baltimore) 2016;95:e4854.
[18] Doorbar J, Quint W, Banks L, Bravo IG, Stoler M, Broker TR, et al. The biology and life-cycle of human papillomaviruses. Vaccine 2012;30(Suppl 5):F55–70.
[19] Clifford G, Franceschi S, Diaz M, Munoz N, Villa LL. Chapter 3: HPV type-distribution in women with and without cervical neoplastic diseases. Vaccine 2006;24(Suppl 3). S3/26-34.
[20] Herrin DM, Coates EE, Costner PJ, Kemp TJ, Nason MC, Saharia KK, et al. Comparison of adaptive and innate immune responses induced by licensed vaccines for Human Papillomavirus. Hum Vaccin Immunother 2014;10:3446–54.
[21] Bissett SL, Godi A, Jit M, Beddows S. Seropositivity to non-vaccine incorporated genotypes induced by the bivalent and quadrivalent HPV vaccines: A systematic review and meta-analysis. Vaccine 2017;35:3922–9.
[22] Lehtinen M, Paavonen J, Wheeler CM, Jaisamrarn U, Garland SM, Castellsague X, et al. Overall efficacy of HPV-16/18 AS04-adjuvanted vaccine against grade 3 or greater cervical intraepithelial neoplasia: 4-year end-of-study analysis of the randomised, double-blind PATRICIA trial. Lancet Oncol 2012;13:89–99.
[23] Kavanagh K, Pollock KG, Cuschieri K, Palmer T, Cameron RL, Watt C, et al. Changes in the prevalence of human papillomavirus following a national bivalent human papillomavirus vaccination programme in Scotland: a 7-year cross-sectional study. Lancet Infect Dis 2017;17:1293–302.
[24] Szarewski A, Skinner SR, Garland SM, Romanowski B, Schwarz TF, Apter D, et al. Efficacy of the HPV-16/18 AS04-adjuvanted vaccine against low-risk HPV types (PATRICIA randomized trial): an unexpected observation. J Infect Dis 2013;208:1391–6.
[25] Canvin M, Sinka K, Hughes G, Mesher D. Decline in genital warts diagnoses among young women and young men since the introduction of the bivalent HPV (16/18) vaccination programme in England: an ecological analysis. Sex Transm Infect 2017;93:125–8.
[26] Brown DR, Kjaer SK, Sigurdsson K, Iversen OE, Hernandez-Avila M, Wheeler CM, et al. The impact of quadrivalent human papillomavirus (HPV; types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine HPV types in generally HPV-naive women aged 16–26 years. J Infect Dis 2009;199:926–35.
[27] Wheeler CM, Kjaer SK, Sigurdsson K, Iversen OE, Hernandez-Avila M, Perez G, et al. The impact of quadrivalent human papillomavirus (HPV; types 6, 11, 16, and 18) L1 virus-like particle vaccine on infection and disease due to oncogenic nonvaccine HPV types in sexually active women aged 16–26 years. J Infect Dis 2009;199:936–44.
[28] Feiring B, Laake I, Christiansen IK, Hansen M, Stalcrantz J, Ambur OH, et al. Substantial decline in prevalence of vaccine-type and non-vaccine type HPV in vaccinated and unvaccinated girls 5 years after implementing HPV vaccine in Norway. J Infect Dis 2018.
[29] Roden RBS, Stern PL. Opportunities and challenges for human papillomavirus vaccination in cancer. Nat Rev Cancer 2018;18:240–54.
[30] Brotherton JML, Bloem PN. Population-based HPV vaccination programmes are safe and effective: 2017 update and the impetus for achieving better global coverage. Best Pract Res Clin Obstet Gynaecol 2018;47:42–58.
[31] Didierlaurent AM, Morel S, Lockman L, Giannini SL, Bisteau M, Carlsen H, et al. AS04, an aluminum salt- and TLR4 agonist-based adjuvant system, induces a transient localized innate immune response leading to enhanced adaptive immunity. J Immunol 2009;183:6186–97.
[32] Matthijnssens J, Otto PH, Ciarlet M, Desselberger U, Van Ranst M, Johne R. VP6-sequence-based cutoff values as a criterion for rotavirus species demarcation. Arch Virol 2012;157:1177–82.
[33] Santos N, Hoshino Y. Global distribution of rotavirus serotypes/genotypes and its implication for the development and implementation of an effective rotavirus vaccine. Rev Med Virol 2005;15:29–56.
[34] Banyai K, Laszlo B, Duque J, Steele AD, Nelson EA, Gentsch JR, et al. Systematic review of regional and temporal trends in global rotavirus strain diversity in the pre rotavirus vaccine era: insights for understanding the impact of rotavirus vaccination programs. Vaccine 2012;30(Suppl 1):A122–30.
[35] Gray J, Vesikari T, Van Damme P, Giaquinto C, Mrukowicz J, Guarino A, et al. Rotavirus. J Pediatr Gastroenterol Nutr 2008;46(Suppl 2):S24–31.
[36] Dennehy PH. Rotavirus vaccines: an overview. Clin Microbiol Rev 2008;21:198–208.
[37] Velasquez DE, Parashar UD, Jiang B. Strain diversity plays no major role in the varying efficacy of rotavirus vaccines: an overview. Infect Genet Evol 2014;28:561–71.
[38] Takeuchi M. Bayesian network meta-analysis suggests a similar effectiveness between a monovalent and a pentavalent rotavirus vaccine: a preliminary report of re-analyses of data from a Cochrane Database Systematic Review. Hum Vaccin Immunother 2014;10:1421–4.
[39] Ruiz-Palacios GM, Perez-Schael I, Velazquez FR, Abate H, Breuer T, Clemens SC, et al. Safety and efficacy of an attenuated vaccine against severe rotavirus gastroenteritis. N Engl J Med 2006;354:11–22.
[40] Linhares AC, Velazquez FR, Perez-Schael I, Saez-Llorens X, Abate H, Espinoza F, et al. Efficacy and safety of an oral live attenuated human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in Latin American infants: a randomised, double-blind, placebo-controlled phase III study. Lancet 2008;371:1181–9.
[41] Madhi SA, Cunliffe NA, Steele D, Witte D, Kirsten M, Louw C, et al. Effect of human rotavirus vaccine on severe diarrhea in African infants. N Engl J Med 2010;362:289–98.
[42] Steele AD, Neuzil KM, Cunliffe NA, Madhi SA, Bos P, Ngwira B, et al. Human rotavirus vaccine Rotarix provides protection against diverse circulating rotavirus strains in African infants: a randomized controlled trial. BMC Infect Dis 2012;12:213.
[43] Vesikari T, Karvonen A, Prymula R, Schuster V, Tejedor JC, Cohen R, et al. Efficacy of human rotavirus vaccine against rotavirus gastroenteritis during the first 2 years of life in European infants: randomised, double-blind controlled study. Lancet 2007;370:1757–63.
[44] Phua KB, Lim FS, Lau YL, Nelson EA, Huang LM, Quak SH, et al. Safety and efficacy of human rotavirus vaccine during the first 2 years of life in Asian infants: randomised, double-blind, controlled study. Vaccine 2009;27:5936–41.
[45] European Medicines Agency (EMA). <http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000639/WC500054789.pdf> [accessed on 2 May 2018].
[46] Ruuska T, Vesikari T. Rotavirus disease in Finnish children: use of numerical scores for clinical severity of diarrhoeal episodes. Scand J Infect Dis 1990;22:259–67.
[47] Serruto D, Bottomley MJ, Ram S, Giuliani MM, Rappuoli R. The new multicomponent vaccine against meningococcal serogroup B, 4CMenB: immunological, functional and structural characterization of the antigens. Vaccine 2012;30(Suppl 2):B87–97.
[48] Vipond C, Care R, Feavers IM. History of meningococcal vaccines and their serological correlates of protection. Vaccine 2012;30(Suppl 2):B10–7.
[49] Wilkins AL, Snape MD. Emerging clinical experience with vaccines against group B meningococcal disease. Vaccine 2018;36(36):5470–6.
[50] Holst J, Oster P, Arnold R, Tatley MV, Naess LM, Aaberge IS, et al. Vaccines against meningococcal serogroup B disease containing outer membrane vesicles (OMV): lessons from past programs and implications for the future. Hum Vaccin Immunother 2013;9:1241–53.
[51] Shirley M, Dhillon S. Bivalent rLP2086 vaccine (Trumenba®): a review in active immunization against invasive meningococcal group B disease in individuals aged 10–25 years. BioDrugs 2015;29:353–61.
[52] Medini D, Stella M, Wassil J. MATS: Global coverage estimates for 4CMenB, a novel multicomponent meningococcal B vaccine. Vaccine 2015;33:2629–36.
[53] Frosi G, Biolchi A, Lo Sapio M, Rigat F, Gilchrist S, Lucidarme J, et al. Bactericidal antibody against a representative epidemiological meningococcal serogroup B panel confirms that MATS underestimates 4CMenB vaccine strain coverage. Vaccine 2013;31:4968–74.
[54] Tozer SJ, Whiley DM, Smith HV, Rockett R, Jennison A, Doyle C, et al. Use of the Meningococcal Antigen Typing System (MATS) to assess Australian

epidemiology and meningococcal strain coverage with multicomponent serogroup B vaccine. Poster presented at 27th ICP, August 24–29, 2013.
[55] Tomei S, Biolchi A, Brunelli B, De Angelis G, Moschioni M, Masignani V, et al. P30. Potential coverage of the BEXSERO® MenB vaccine on non-B meningococci. <http://neisseria.org/ipnc/2014/IPNC_2014_abstracts.pdf> [accessed on 8 May 2018].
[56] Hong E, Giuliani MM, Deghmane AE, Comanducci M, Brunelli B, Dull P, et al. Could the multicomponent meningococcal serogroup B vaccine (4CMenB) control Neisseria meningitidis capsular group X outbreaks in Africa? Vaccine 2013;31:1113–6.
[57] Ladhani SN, Giuliani MM, Biolchi A, Pizza M, Beebeejaun K, Lucidarme J, et al. Effectiveness of Meningococcal B Vaccine against Endemic Hypervirulent Neisseria meningitidis W Strain, England. Emerg Infect Dis 2016;22:309–11.
[58] Joint Committee on Vaccination and Immunisation (JCVI). JCVI position statement on use of Bexsero® meningococcal B Vaccine in the UK. <https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/294245/JCVI_Statement_on_MenB.pdf> [accessed on 8 May 2018].
[59] Tinsley CR, Nassif X. Analysis of the genetic differences between Neisseria meningitidis and Neisseria gonorrhoeae: two closely related bacteria expressing two different pathogenicities. Proc Natl Acad Sci U S A 1996;93:11109–14.
[60] Edwards JL, Jennings MP, Seib KL. Neisseria gonorrhoeae vaccine development: hope on the horizon? Curr Opin Infect Dis 2018;31:246–50.
[61] Whelan J, Klovstad H, Haugen IL, Holle MR, Storsaeter J. Ecologic Study of Meningococcal B Vaccine and Neisseria gonorrhoeae Infection. Norway. Emerg Infect Dis 2016;22:1137–9.
[62] Petousis-Harris H, Paynter J, Morgan J, Saxton P, McArdle B, Goodyear-Smith F, et al. Effectiveness of a group B outer membrane vesicle meningococcal vaccine against gonorrhoea in New Zealand: a retrospective case-control study. Lancet 2017;390:1603–10.
[63] Centers for Disease Control and Prevention (CDC). Types of Influenza Viruses. <https://www.cdc.gov/flu/about/viruses/types.htm> [accessed on 19 June 2018].
[64] Orsi A, Ansaldi F, de Florentiis D, Ceravolo A, Parodi V, Canepa P, et al. Cross-protection against drifted influenza viruses: options offered by adjuvanted and intradermal vaccines. Hum Vaccin Immunother 2013;9:582–90.
[65] Camilloni B, Basileo M, Valente S, Nunzi E, Iorio AM. Immunogenicity of intramuscular MF59-adjuvanted and intradermal administered influenza enhanced vaccines in subjects aged over 60: A literature review. Hum Vaccin Immunother 2015;11:553–63.
[66] Domnich A, Arata L, Amicizia D, Puig-Barbera J, Gasparini R, Panatto D. Effectiveness of MF59-adjuvanted seasonal influenza vaccine in the elderly: A systematic review and meta-analysis. Vaccine 2017;35:513–20.
[67] Baldo V, Baldovin T, Pellegrini M, Angiolelli G, Majori S, Floreani A, et al. Immunogenicity of three different influenza vaccines against homologous and heterologous strains in nursing home elderly residents. Clin Dev Immunol 2010;2010:517198.
[68] Cowling BJ, Ng S, Ma ES, Fang VJ, So HC, Wai W, et al. Protective efficacy against pandemic influenza of seasonal influenza vaccination in children in Hong Kong: a randomized controlled trial. Clin Infect Dis 2012;55:695–702.
[69] Chada KE, Forshee R, Golding H, Anderson S, Yang H. A systematic review and meta-analysis of cross-reactivity of antibodies induced by oil-in-water emulsion adjuvanted influenza H5N1 virus monovalent vaccines. Vaccine 2017;35:3162–70.
[70] Leroux-Roels I, Borkowski A, Vanwolleghem T, Drame M, Clement F, Hons E, et al. Antigen sparing and cross-reactive immunity with an adjuvanted rH5N1 prototype pandemic influenza vaccine: a randomised controlled trial. Lancet 2007;370:580–9.
[71] Leroux-Roels I, Bernhard R, Gerard P, Drame M, Hanon E, Leroux-Roels G. Broad Clade 2 cross-reactive immunity induced by an adjuvanted clade 1 rH5N1 pandemic influenza vaccine. PLoS One 2008;3:e1665.
[72] Thomson CA, Wang Y, Jackson LM, Olson M, Wang W, Liavonchanka A, et al. Pandemic H1N1 Influenza Infection and Vaccination in Humans Induces Cross-Protective Antibodies that Target the Hemagglutinin Stem. Front Immunol 2012;3:87.
[73] Li GM, Chiu C, Wrammert J, McCausland M, Andrews SF, Zheng NY, et al. Pandemic H1N1 influenza vaccine induces a recall response in humans that favors broadly cross-reactive memory B cells. Proc Natl Acad Sci U S A 2012;109:9047–52.
[74] Fernandez-Garcia MD, Mazzon M, Jacobs M, Amara A. Pathogenesis of flavivirus infections: using and abusing the host cell. Cell Host Microbe 2009;5:318–28.
[75] Kollaritsch H, Krasilnikov V, Holzmann H, Karganova G, Barrett A, Süss J, et al. Background Document on Vaccines and Vaccination against Tick-borne Encephalitis (TBE). <http://www.who.int/immunization/sage/6_TBE_backgr_18_Mar_net_apr_2011.pdf> [accessed on 10 May 2018].
[76] Domnich A, Panatto D, Arbuzova EK, Signori A, Avio U, Gasparini R, et al. Immunogenicity against Far Eastern and Siberian subtypes of tick-borne encephalitis (TBE) virus elicited by the currently available vaccines based on the European subtype: systematic review and meta-analysis. Hum Vaccin Immunother 2014;10:2819–33.
[77] Lobigs M, Diamond MS. Feasibility of cross-protective vaccination against flaviviruses of the Japanese encephalitis serocomplex. Expert Rev Vaccines 2012;11:177–87.
[78] Priyamvada L, Hudson W, Ahmed R, Wrammert J. Humoral cross-reactivity between Zika and dengue viruses: implications for protection and pathology. Emerg Microbes Infect 2017;6:e33.
[79] Mansfield KL, Horton DL, Johnson N, Li L, Barrett AD, Smith DJ, et al. Flavivirus-induced antibody cross-reactivity. J Gen Virol 2011;92:2821–9.
[80] Schuller E, Klade CS, Heinz FX, Kollaritsch H, Rendi-Wagner P, Jilma B, et al. Effect of pre-existing anti-tick-borne encephalitis virus immunity on neutralising antibody response to the Vero cell-derived, inactivated Japanese encephalitis virus vaccine candidate IC51. Vaccine 2008;26:6151–6.
[81] Chidumayo NN, Yoshii K, Kariwa H. Evaluation of the European tick-borne encephalitis vaccine against Omsk hemorrhagic fever virus. Microbiol Immunol 2014;58:112–8.
[82] Brookes SM, Parsons G, Johnson N, McElhinney LM, Fooks AR. Rabies human diploid cell vaccine elicits cross-neutralising and cross-protecting immune responses against European and Australian bat lyssaviruses. Vaccine 2005;23:4101–9.
[83] Malerczyk C, Freuling C, Gniel D, Giesen A, Selhorst T, Muller T. Cross-neutralization of antibodies induced by vaccination with Purified Chick Embryo Cell Vaccine (PCECV) against different Lyssavirus species. Hum Vaccin Immunother 2014;10:2799–804.
[84] Malerczyk C, Selhorst T, Tordo N, Moore S, Muller T. Antibodies induced by vaccination with purified chick embryo cell culture vaccine (PCECV) cross-neutralize non-classical bat lyssavirus strains. Vaccine 2009;27:5320–5.
[85] Wong SS, Webby RJ. Traditional and new influenza vaccines. Clin Microbiol Rev 2013;26:476–92.
[86] Wood P. Understanding immunology. 2nd ed. Harlow, England: Pearson Education Limited; 2006.
[87] Frank SA. Immunology and evolution of infectious disease. Princeton, New Jersey: Princeton University Press; 2002.
[88] Leo O, Cunningham A, Stern PL. Vaccine immunology. In: Garçon N, Stern PL, Cunningham AL, editors. Understanding Modern Vaccines: Perspectives in Vaccinology. Amsterdam: Elsevier; 2011. p. 25–59.
[89] Mason D. A very high level of crossreactivity is an essential feature of the T-cell receptor. Immunol Today 1998;19:395–404.
[90] Sewell AK. Why must T cells be cross-reactive? Nat Rev Immunol 2012;12:669–77.
[91] Arstila TP, Casrouge A, Baron V, Even J, Kanellopoulos J, Kourilsky P. A direct estimate of the human alphabeta T cell receptor diversity. Science 1999;286:958–61.
[92] Yin Y, Mariuzza RA. The multiple mechanisms of T cell receptor cross-reactivity. Immunity 2009;31:849–51.
[93] Kim JS, Laskowich ER, Arumugham RG, Kaiser RE, MacMichael GJ. Determination of saccharide content in pneumococcal polysaccharides and conjugate vaccines by GC-MSD. Anal Biochem 2005;347:262–74.
[94] Sautto GA, Kirchenbaum GA, Ross TM. Towards a universal influenza vaccine: different approaches for one goal. Virol J 2018;15:17.
[95] Siegrist C. Vaccine immunology. In: Plotkin SA, Orenstein WA, Offit PA, editors. Vaccines. Elsevier Health Sciences; 2013. p. 14–32.
[96] Garcon N, Di Pasquale A. From discovery to licensure, the Adjuvant System story. Hum Vaccin Immunother 2017;13:19–33.
[97] Fox CB, Kramer RM, Barnes VL, Dowling QM, Vedvick TS. Working together: interactions between vaccine antigens and adjuvants. Ther Adv Vaccines 2013;1:7–20.
[98] Di Pasquale A, Preiss S, Tavares Da Silva F, Garcon N. Vaccine adjuvants: from1920 to 2015 and beyond. Vaccines (Basel) 2015;3:320–43.
[99] Lee S, Nguyen MT. Recent advances of vaccine adjuvants for infectious diseases. Immune Netw 2015;15:51–7.
[100] Webby RJ, Weaver EA. Centralized consensus hemagglutinin genes induce protective immunity against H1, H3 and H5 influenza viruses. PLoS One 2015;10:e0140702.

Glossary

Cross-protection [in vaccinology]: clinical protection elicited by a vaccine against a non-vaccine type microorganism
Cross-reactivity [in vaccinology]: immunostimulation elicited by a vaccine against a non-vaccine type microorganism
Genotype: genetic constitution of an individual organism
Serotype: a serologically distinguishable strain of a microorganism
Subtype: a division of a type of microorganism below the species or strain level – typically identified in variations in specific target antigens – not requiring serology for distinction.