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A literature review and evidence-based evaluation of the Dutch national immunisation schedule yield possibilities for improvements

A.J.M. Pluijmaekers [a,1], A. Steens [a,*,1], H. Houweling [a], N.Y. Rots [a], K.S.M. Benschop [a], R.S. van Binnendijk [a], R. Bodewes [a], J.G.M. Brouwer [a], A. Buisman [a], E. Duizer [a], C.A.C.M. van Els [a,b], J.M. Hament [a], G. den Hartog [a,c], P. Kaaijk [a], K. Kerkhof [a], A.J. King [a], F.R.M. van der Klis [a], H. Korthals Altes [a], N.A.T. van der Maas [a], D.L. van Meijeren [a], M. Middeldorp [a], S.D. Rijnbende-Geraerts [d], E.A.M. Sanders [a,e], I.K. Veldhuijzen [a], E. Vlaanderen [f], A.C.G. Voordouw [a], E.R.A. Vos [a], J. de Wit [a], T. Woudenberg [a], J.A. van Vliet [a], H.E. de Melker [a]

[a] Center for Infectious Disease Control (CIb), National Institute for Public Health and the Environment (RIVM), The Netherlands
[b] Faculty of Infectious Diseases and Immunology, Department of Biomolecular Health Sciences, Faculty of Veterinary Medicine, Utrecht University, The Netherlands
[c] Laboratory of Medical Immunology, Radboud UMC, Nijmegen, The Netherlands
[d] Public Health, Municipality of Utrecht, The Netherlands
[e] Department of Paediatric Immunology and Infectious Diseases, Wilhelmina Children's Hospital and University Medical Centre Utrecht, The Netherlands
[f] Municipal Health Service of Hollands Noorden, The Netherlands

A B S T R A C T

National Immunisation Programmes (NIPs) develop historically. Its performance (disease incidences, vaccination coverage) is monitored. Reviewing the schedule as a whole could inform on further optimisation of the programme, i.e., providing maximal protection with the lowest number of doses. We systematically evaluated the performance and strategies of the Dutch pathogen-specific NIP schedules through literature review, assessment of surveillance data and expert opinions.

Pathogen-specific vaccinations were categorised according to their strategy of protection: I) elimination or eradication, II) herd immunity or III) 'only' individual protection. The schedule of each vaccine-component was evaluated based on fixed criteria: 1. Is the achieved protection adequate? 2. Is the intended protection achieved? 3. Does the programme include too many or too few doses? 4. Is the timing optimal or acceptable? and 5. Are there drawbacks of the NIP for (part of) the population? Identified issues were explored using surveillance data and literature.

Using fixed criteria facilitated comparison between pathogens and revealed opportunities to optimise the Dutch NIP by: i. Reducing the number of polio and tetanus vaccinations; ii. prolonging the interval between diphtheria, pertussis, tetanus, polio, hepatitis B, and Hib vaccine doses for improved effectiveness; iii. Expedite the second measles vaccination from 9 to 2–4 years of age to offer unvaccinated children and primary vaccine failures an earlier chance to be protected; and iv. Delaying the second mumps vaccination to enhance protection in adolescents/young adults. No schedule adaptations were deemed necessary for the vaccines against HPV, rubella, pneumococcal disease, and meningococcal disease. Based on this evaluation the NITAG advised to move the DTaP-IPV-HBV-Hib-booster from age 11 to 12 months, the second MMR-dose from 9 to 2–4 years, replace the Tdap-IPV at 4 years with a Tdap at 5–6 years and move the dt-IPV from 9 to 14 years. Implementation of these changes is planned for 2025.

Introduction

The Dutch National Immunisation Programme (NIP) for children up to 18 years of age started in 1957 and currently includes vaccines against (severe disease caused by) 13 pathogens (see Table 1). Combination vaccines are used and most vaccines require two or three primary doses and one or more boosters (referred to as, e.g., 2 + 1 for 2 primary doses and 1 booster dose). The NIP started with a limited number of vaccines to which throughout years vaccines have been added and schedules have changed. The performance of each individual vaccine-component (e.g., disease incidence) is monitored but evaluating the performance of the program as a whole could lead to further optimisation, i.e., providing maximal protection with the lowest number of doses. Ideally, such evaluations should be done regularly by National Immunisation

* Corresponding author at: RIVM, Antonie van Leeuwenhoeklaan 9, 3721 MA Bilthoven, The Netherlands.
E-mail address: anneke.steens@rivm.nl (A. Steens).
[1] Contributed equally.

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Technical Advisory Groups (NITAGs).

The aim of the Dutch NIP is to protect the population against serious infectious diseases and to achieve a fair distribution of care [1]. Depending on the pathogen, the protection is achieved preferentially by: I) eradication or elimination of the pathogen or disease, II) achieving herd immunity, i.e., protection of non-vaccinated groups by interrupting transmission, or III) individual protection of as many vulnerable individuals as possible. For some pathogens, the World Health Organization (WHO) has set elimination or eradication goals. Except for smallpox, eradication has not been reached (yet). For most pathogens, herd immunity is a more realistic strategy to protect the population, but vaccine uptake needs to be high enough. Otherwise, only individual protection is feasible.

In the Netherlands, the vaccination coverage is about 90 % for most pathogens, with the exception of HPV (about 45–65 %) and adolescent meningococcal serogroup ACWY vaccination (around 82 %) [2].

Table 1
Overview of the vaccinations in the evaluated NIP, their prevention strategy, and their vaccination schedules. For strategy, preferentially protection is achieved through I: eradication or elimination, if not reachable, II: reaching herd immunity, if also not reachable, III: through individual protection. The next level is thus included in the ones above, i.e., individual protection is also included in aiming for elimination or herd immunity. Note, from 2024, rotavirus vaccination is implemented at 6–9 weeks and 3 months, but as, at the time of evaluation, this vaccine was not yet implemented, rotavirus is not discussed here any further.

Disease	Included strain/ type in current NIP	Start NIP	Strategy of inclusion in NIP	Exposure in current schedule									
				Pre birth[1]	2m[2]	3m	5m	11m	14m	4y	9y	10y	14y
Diphtheria[5, 6]	Diphtheria toxoid	1957	Herd immunity	Pas	Prim	Prim	Prim	Boos		Boos[7]	Boos		
Pertussis[5]	Pertussis toxoid, fha, pertactin, *fim2* and *fim3*	1952	Individual protection	Pas	Prim	Prim	Prim	Boos		Boos[7]			
Tetanus[3, 5, 6]	Tetanus toxoid	1952	Individual protection	Pas	Prim	Prim	Prim	Boos		Boos[7]	Boos		
Poliomyelitis[5]	Inactivated virus types 1 (Mahoney), 2 (MEF-1) and 3 (Saukett)	1957	Eradication		Prim	Prim	Prim	Boos		Boos	Boos		
Hepatitis B[4, 5]	Hepatitis B surface antigen	2011 (since 2003 for risk groups)	Individual protection, but secondary goal to reach European elimination		Prim	Prim	Prim	Boos					
Haemophilus influenzae serotype B[5]	PRP-OMC of *Neisseria meningitidis*. Hib Ross-strain	1993	Individual protection. Secondarily to decrease circulation		Prim	Prim	Prim	Boos					
Pneumococcus	Serotypes 1, 4, 5, 6B, 7F, 9 V, 14, 18C, 19F, 23F	2006 (PCV7; PCV10[6] since 2011; PCV15 implementation from autumn 2024 onwards)	Herd immunity			Prim	Prim	Boos					
Meningococcus	Serogroups ACWY	2002 (MenC; 14m only); tetravalent (MenACWY[6]) since 2018	Herd immunity						Prim				Boos
Mumps[5]	Jeryl Lynn strain (Genotype A)	1987	Individual protection or herd immunity (see issues)						Prim		Boos		
Measles[5]	Based on Edmondson isolate	1976 (stand-alone), 1987 MMR	Eradication						Prim		Boos		
Rubella[5]	RA 27/3 strain	1974 (stand-alone), 1987 MMR	Eradication						Prim		Boos		
Human papillomavirus	Types 16 and 18	2010 (girls), 2020 (boys)	Herd immunity									Prim/ Boos	

Pas = passive immunisation, Prim = primary series, Boos = Booster.

[1] Since late 2019, a maternal Tdap vaccination (MPV) is offered at or after 22 weeks gestation (coverage ≈70 %). Consequently, the main schedule was changed in 2020 from a 3 + 1 schedule at 2, 3, 4 and 11 months to a 2 + 1 schedule at 3, 5, and 11 months.

[2] Only offered to specific groups, e.g., no or late maternal Tdap vaccination, prematurely born infants, infants born from immune compromised mothers, hepatitis B high-risk group.

[3] Post-exposure prophylaxis (tetanus toxoid vaccination and tetanus immune globulins) is an essential element of the protection against tetanus; this is not further discussed here.

[4] Since 2003, the following risk groups receive an extra dose of DTaP-IPV-HBV-Hib at 2 months of age:
- Children with at least one parent born in a country with intermediate to high prevalence of hepatitis B.
- Infants of hepatitis B positive mothers. These infants additionally receive immunoglobulin and a dose of single hepatitis B vaccine at birth.

[5] Provided as combination vaccine: DTaP-IPV-HBV-Hib at 3, 5, 11 months, TdaP-IPV at 4 years, DT-IPV at 9 years, and MMR at 14 months and 9 years.

[6] Note that the used MenACWY vaccine, the Tdap used for maternal vaccination, and one of the pneumococcal serotypes in PCV10, are conjugated to a tetanus-toxoid carrier protein. Similarly, eight pneumococcal serotypes in PCV10 are conjugated to a diphtheria-toxoid carrier. These carrier proteins might elicit a primary or booster immune response.

[7] At 4 and 9 years, the pertussis, diphtheria and tetanus components are low-dose in comparison to the primary vaccinations.

However, vaccination coverage is lower among orthodox-reformed individuals, who live socio-geographically clustered [3], and in certain subgroups (e.g., those with anthroposophical views and people with a non-Western migration background).

We here present the applied method and summary of a systematic evaluation of the protection strategy and performance of the pathogen-specific vaccination schedules. We present changes to the schedule that may further optimise the NIP's performance [1].

Method

A broad group of vaccination experts was composed, including epidemiologists, immunologists, medical doctors, microbiologists, and infectious disease modellers, mainly working at the Center for Infectious Disease Control (CIb) of the National Institute for Public Health and the Environment (RIVM). The CIb has the task to coordinate the control of infectious diseases including providing background information to the NITAG. The responsibility for purchasing vaccines is not part of the CIb. The expert group gathered in 2021–2022 for ~15 meetings to coordinate the evaluation process and discuss findings. Pathogen-specific subgroups performed non-systematic but thorough reviews of literature relevant for the Dutch setting through searches in PubMed, Medline and Google Scholar. Additional information was obtained from other public health institutes, ECDC's vaccine scheduler, surveillance, and research where available.

For each pathogen, the Dutch NIP was evaluated according to the protection strategy (eradication/elimination, herd immunity, individual protection) using the following criteria/questions:

1. Is the achieved protection adequate for all those intended to be protected?
2. Is the applied vaccination strategy optimal, i.e. providing maximal protection with the lowest number of doses?
3. Does the programme include too much or too little?
4. Is the timing of immunisations using combination vaccines optimal or at least acceptable?
5. Are there important drawbacks to the NIP? For the population as a whole? For those who opt out? How are these drawbacks weighed against the advantages of the programme and its components?

Formulation of the criteria was informed by discussions on aiming to have an immunisation schedule with the least doses [4–6]. The execution of the programme was not evaluated. Using the criteria, issues that could be overcome through a schedule change were identified by the subgroups and discussed with the expert group. The structured evaluation, performed per pathogen, provided a clear overview of prevention strategies, disease epidemiology and identified issues. Discussing the subgroups' findings with the entire group using the fixed set of criteria, facilitated comparison between pathogens. The findings were summarised in an extensive report [1]. Formulating conclusions on potential NIP changes was not part of the group's mandate; the NITAG of the Netherlands used the report and additionally evaluated the use of combination vaccines to advise the Ministry of Health on possible optimisation of the NIP [1,7].

Results

The following paragraphs briefly discuss the findings per pathogen. Table 2 summarises the issues (Roman numbers) that were found for each criterium (Arabic numbers), which are referenced to in the text as "(1:i)". Proposals for changes to optimise the pathogen-specific schedules are presented in Fig. 1.

Diphtheria

Because diphtheria can lead to hospitalisation and/or death, vaccination is aimed at offering lifelong protection against disease by individual protection and herd immunity [8]. This strategy has been successful since the diphtheria incidence is low (≤7 cases yearly since 2000), with no reported deaths [9]. However, the orthodox-reformed population is inadequately protected (1:ii).

While diphtheria antibodies are long-lasting, levels do decline after vaccination [10] (1:i). Boosters later in childhood are thus important to maintain long-lasting protection [11]. Several childhood vaccines against other diseases contain diphtheria-toxoid or diphtheria-toxin cross-reactive material (CRM_{197}) carrier proteins. While these proteins may stimulate the immune response, their immunogenic effects are currently not taken into account for licensing. Furthermore, the used carrier proteins may change as a result of compulsory European tenders (3:v). Vaccines with diphtheria carrier proteins are thus not considered a vaccine dose. Based on the high seroprevalence in children [10], the number of childhood (booster) doses seems sufficient (3:vi). However, the interval between doses could be extended for vaccine effectiveness to persist longer, thereby prolonging protection into adulthood (4:vi, viii). Specifically, the booster at 4 years might be postponed or skipped, and a booster just before the age of 18 years could be considered.

Booster doses during adulthood are necessary for adequate persistent protection [10,12] (1:i) and are recommended every ten years [8]. Despite different correlates of protection for short- and long-term protection [13,14] (1:iii,iv), immunogenicity studies suggest that extending the interval between boosters is possible while still providing protection [13,14] (3:vii).

Pertussis

The strategy of the pertussis vaccination program is to provide individual protection to children <5 years of age against severe disease leading to hospitalisation and/or death. Disease incidence is relatively high among young, not yet (fully) vaccinated infants. Annually, 0–2 pertussis-related deaths occurred in the Netherlands, predominantly among children <1 year [9]. In 2024 up to and including July, there were already six infant deaths due to pertussis [15]. This indicates a suboptimal vaccination strategy (2:ii). Furthermore, seroprevalence data suggest that pertussis circulation increases in older children and adults, who may transmit to infants (2,3:ii). To better protect infants, maternal pertussis vaccination (MPV) was introduced in 2019. The MPV was shown to be safe [16] (1:i).

Current infants' 2 + 1 series after MPV was based on immunogenicity data [17]. Infants of mothers who have not received MPV or with potentially limited protection from MPV (see Table 1) receive 3 + 1 doses. The necessity of the additional 2-month dose (3:iii) is evaluated in immunogenicity studies in preterm infants and in (infants of) women using immunosuppressive medication [18,19].

The current schedule results in high antibody levels and strong cellular responses [20–22]. However, high T-cell-derived cytokine levels may increase the frequency and severity of side effects [20–22]. Fewer doses and longer intervals seem appropriate (4:iv); the (high dose) booster may be delayed from 11 to 12–18 months of age. Based on seroprevalence and incidence data from Sweden and France [23,24], the low-dose booster at 4 years could be postponed to age 5–6.

The increased pertussis circulation among older children and adults might be related to (an interplay of) waning immunity and pathogen adaptation resulting from the long term vaccination policy leading to vaccine-antigen-deficient *B. pertussis* strains [25]. Evaluation of the pertussis-containing vaccines currently in use and of their potential effects on the increase in vaccine-antigen-deficient strains and on transmission, is out of scope for this review.

Tetanus

The aim of tetanus vaccination is individual protection against disease at all ages as it can lead to death or severe disease requiring

Table 2
Overview of the issues of each NIP pathogen (rows; Roman numbers) that were identified using the assessment criteria (columns; Arabic numbers). See the methods section for the full questions per criterium. If no issue was identified for a criterium, not applicable (NA) was registered. Note that some issues fit with several assessment criteria.

	Assessment criteria				
	1. Adequate protection?	2. Strategy not optimal?	3. Too much or little?	4. Timing	5. Important drawbacks?
Diphtheria	i) Antibody levels decline in adulthood. ii) Low protection of the orthodox-reformed population. iii) Uncertain cut-off for protective antibody levels. iv) Influence of cellular immunity unknown.	NA	v) Impact of vaccines with diphtheria carrier proteins? vi) NIP boosters could be lowered in amount or spread out more. vii) Optimal booster intervals for adults?	viii) Increased interval between NIP boosters could prolong protection.	NA
Pertussis	i) Is the MPV safe and effective?	ii) Public health importance of increased incidence in older children and adults?	ii) See criterium 2. iii) Additional vaccination at 2 months still necessary in absence of valid MPV or for hepatitis B risk group children?	iv) Can intervals between primary series and 1st booster, and the 1st and 2nd booster be prolonged?	NA
Tetanus	i) Low protection of the orthodox-reformed population. ii) Uncertain cut-off for protective antibody levels. iii) Influence of cellular immunity unknown.	NA	iv) Impact of vaccines with tetanus carrier proteins? v) The number of booster doses could be lowered. vi) Are booster doses needed in adulthood?	vii) Time between the boosters could be prolonged.	NA
Polio	i) Low protection of the orthodox-reformed population. ii) Is the poliovirus surveillance system appropriate?	iii) Should there be a switch from standard IPV to sIPV? *$	iv) The number of booster doses could be reduced.	v) Time between the IPV booster doses could be extended.	NA
Hepatitis B	i) Hepatitis B vaccination for risk groups needs continues attention and monitoring. *	NA	ii) Can doses be reduced for children of mothers with a chronic HBV infection or if mother did not receive MPV?	iii) Can interval between birth- and 2nd dose be increased to 3 months for children of mothers with a chronic HBV infection?	NA
H. influenzae serotype b	i) Direct and indirect protection seem incomplete. ii) Do changes to the schedule and vaccine contribute to the recent increase in invasive Hib disease cases?	iii) Is the booster given too early?	iv) Changes to the schedule from 4 to 3 doses should be evaluated.	iii) See criterium 2.	v) Does replacement play a role for *H. influenzae?* *
Pneumococcus	i) Should the preventive potential of PCV10 vs. more valent PCVs be evaluated?	NA	i) See criterium 1. ii) Could a 1+1 schedule be applicable?	iii) Can the booster dose be given at an older age?	i) See criterium 1.
Meningococcus	NA	NA	i) Is it possible to omit the 14-months dose? ii) MenB vaccination is available but not used.	iii) Could the 2nd dose be given at an earlier age?	NA
Mumps	i) How to weight the increase of relatively mild cases in vaccinated adolescent and young adults against the success of the NIP in protecting young children?	ii) If further protection of adolescents and young adults is deemed within the scope of the NIP, the strategy is not optimal.	ii) See criterium 2.	iii) Could postponing the 2nd dose of mumps vaccine to age 12–14, lengthen the period of protective immunity?	iv) Should preventing outbreaks among students/adolescents have consequences for the NIP? v) Does benefit for the full population outweigh the possible negative effect of increased age at infection in communities with low coverage?

(*continued on next page*)

Table 2 (*continued*)

	Assessment criteria				
	1. Adequate protection?	2. Strategy not optimal?	3. Too much or little?	4. Timing	5. Important drawbacks?
Measles	i) Children in areas with low coverage who are too young to be vaccinated, are at risk during an outbreak of measles.	ii) Increased risk of measles outbreaks due to clustering of unvaccinated individuals.	NA	i) See criterium 1. iii) Interval between 1st and 2nd MMR doses can be shorter (at 2–4 years), protecting children with primary vaccine failure after 1st dose.	iv) Because exposure to measles is rare but increases during an outbreak, unvaccinated persons are often first infected as adults, when risk of complications is higher.
Rubella	i) In areas with low coverage, unborn children of pregnant women without immunity to rubella are at risk of complications of rubella in case of an outbreak.	NA	ii) A 2nd dose is not needed to increase protection.	NA	i) See criterium 1.
HPV	i) Will the effectiveness against only vaccine-targeted HPV types be sufficient to prevent HPV-related cancer? * ii) Is cross-protection against non-vaccine hrHPV types sufficient to prevent HPV-related cancer from these types?	iii) Low vaccination coverage in girls.	iv) No issue, but good to revisit this question in the near future.	NA	NA

Footnotes:
*: Issue not discussed in this manuscript as we mainly focussed on issues that are relevant for the schedule itself.
$ sIPV = IPV based on attenuated Sabin virus strains.

hospitalisation. In the period 2009–2022, there have been three tetanus-related deaths in the Netherlands. The annual number of tetanus cases has been below five [9] and mainly occur among individuals born before mass vaccination and who received insufficient post-exposure prophylactic care. These data suggest that individual protection is being achieved. However, seroprevalence in people from the orthodox-reformed population is low (1:i).

The low tetanus incidence and high tetanus antitoxin antibody concentrations in young children indicate that the booster dose at 4 years of age may be redundant (3:v) or that booster doses may be postponed (4:vii). Furthermore, the current NIP uses several vaccines in which antigens are conjugated to tetanus-toxoid (Table 1). The conjugates may be somewhat immunogenic but are not standardised as antigen [26]. Furthermore, as is the case for diphtheria-based carrier proteins, the availability of tetanus-toxoid carrier proteins in the NIP-vaccines may change as a result of compulsory European tenders (3:iv).

Uncertainties about the correlate of protection for tetanus hamper assessment of population-wide protection [27,28] (1:ii,iii). However, immunogenicity studies have shown that tetanus vaccines induce robust cellular responses including memory B cells [29,30] and good humoral immunity lasting for at least two decades [12,31,32]. This implies that the first adult booster can be offered at a later age, and that the current interval of 10 years may be prolonged (3:vi).

Poliomyelitis

Poliomyelitis vaccination is meant to prevent disease among all ages as infection can lead to death or permanent disability at all ages. Furthermore, the WHO, as part of the Global Polio Eradication Initiative, aims to eradicate poliovirus around the world [33]. The last poliomyelitis outbreak in the Netherlands was in 1992–1993 among 71 unvaccinated individuals, and led to two deaths [9]. Since 1994, the Netherlands has been declared free of poliomyelitis, implying that the vaccination strategy works well. Additionally, immunosurveillance shows high levels of neutralizing anti-poliovirus antibodies in the population and slow waning [34]. However, the orthodox-reformed population is inadequately protected (1:i). Furthermore, because the Netherlands has facilities that process infective wildtype polio virus, sensitive surveillance including clinical and sewage activities remains necessary to early detect introductions (1:ii).

Schedules with ≥3 doses of inactivated polio vaccine (IPV) are sufficient for protective immunity against paralytic disease [35], but the impact on infection and transmission might be more limited. The Dutch NIP contains five or six IPV doses (Table 1), with the last dose at 9 years of age. The current number of vaccinations may therefore be reduced (3:iv). However, data indicate that around 20 years after vaccination, antibody titres start to drop below the level considered protective (cellular immunity was not taken into account); it is not clear if that leads to increased risk of disease [34,36]. As the timing of booster doses is flexible, extending the vaccination interval might prolong protection further into older adulthood with four doses (4:v).

Hepatitis B

The goal of vaccination against hepatitis B virus (HBV), is to prevent both acute and chronic HBV infection and its long-term sequelae through individual protection. Moreover, the WHO European region aims to be hepatitis B-free by 2030.

Thanks to the highly immunogenic HBV-vaccines with long-lasting protection, the NIP offers adequate protection against HBV. Still, children from mothers with a chronic HBV-infection remain an important risk group. However, adherence to antenatal screening is very high in the Netherlands, as is use of prophylactic IgG treatment and additional vaccination for infants of HBV-positive mothers at birth.

The timing of HBV vaccination is generally flexible; a large meta-analysis found no differences in incidence of HBV-infections between

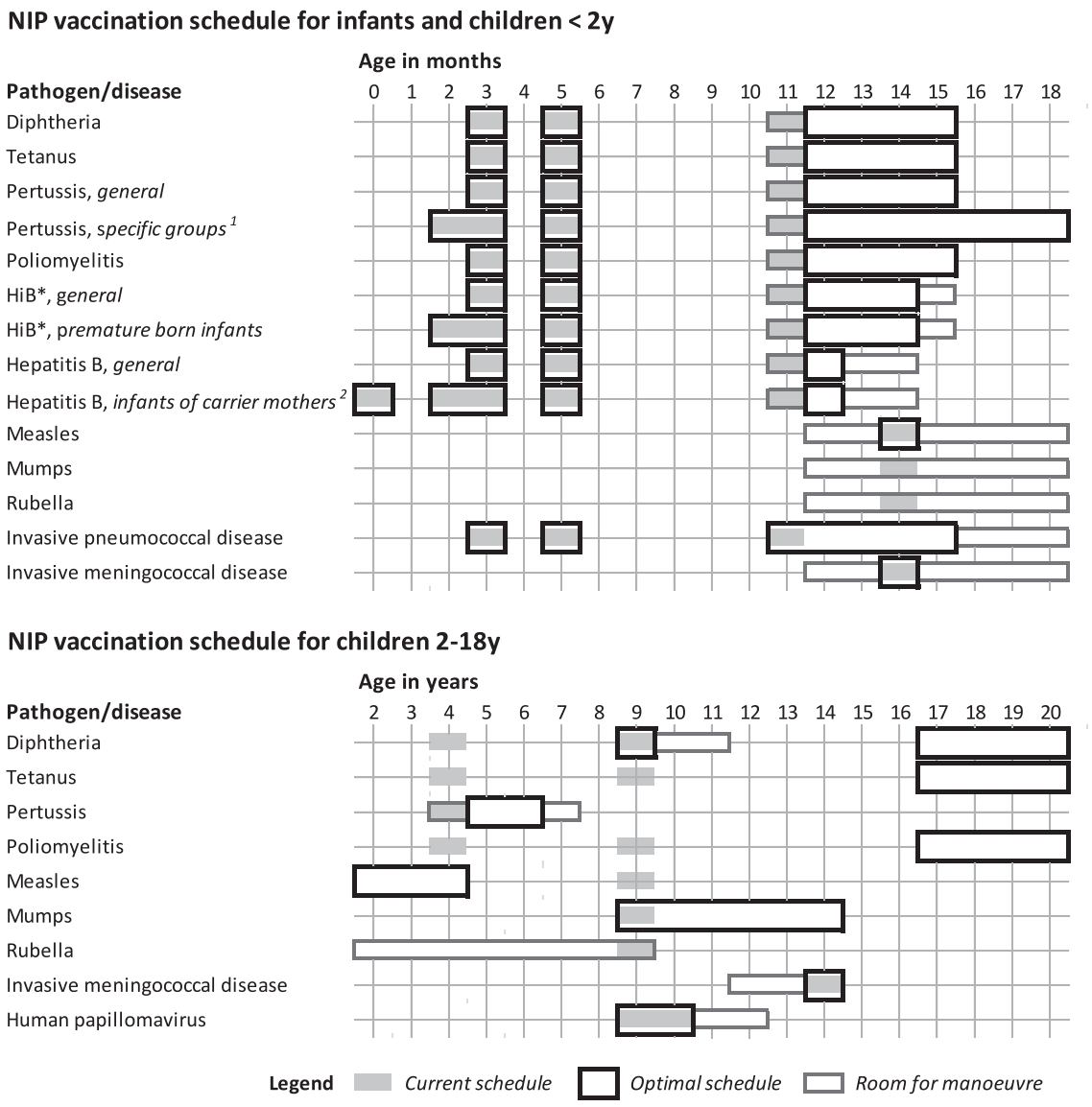

Fig. 1. Current and suggested NIP vaccination schedule. Adapted from (1) according to recent updates. Footnote: In case no "current schedule" moment is indicated in the period for the "optimal schedule" or for "room for manoeuvre", the vaccination moment is to be added. If the current vaccination moment is not part of the "optimal schedule" or the period "room for manoeuvre", the vaccination moment is to be discontinued. In all other cases, vaccination moments will remain, but may have to be moved to fit within the most optimal window. [1] Premature born infants, infants born to mothers not vaccinated during pregnancy or to mothers with immune disease. [2] Optimal schedule to be discussed in conjunction with healthcare factors and logistics.

different schedules, dosages and vaccine types [37]. To achieve protection, for the general population, a 2 + 1 schedule is sufficient. For infants of HBV-positive mothers, the birth-dose is essential; subsequently, the 3 + 1 schedule is followed to prevent errors. WHO recommends 2 or 3 doses after the birth dose [38]. Omitting the 2 months-dose of the 3+1 schedule and offering the second dose at 3 months, thereby following the standard 2 + 1 schedule, would diminish the number of doses (3:ii). However, there is insufficient data to support stretching the interval between the first two doses, while adequate protection of this risk group is essential given the high risk of chronic HBV infection (4:iii).

Currently, infants of HBV-positive mothers or of mothers who had not received MPV receive the 2 months-dose through the combination vaccine DTaP-IPV-Hib-HBV. As a 2 + 1 schedule leads to protection for up to at least 30 years [39], the HBV-component at 2 months could be omitted for infants of HBV-negative mothers that did not receive the MPV (3:ii). For infants of HBV-positive mothers that have received MPV, a stand-alone HBV-vaccine could be given instead of the combination vaccine.

Haemophilus influenzae serotype b

Vaccinating against *Haemophilus influenzae* serotype b (Hib) is aimed to provide individual protection against invasive disease among children <5 years of age, the most vulnerable group. A second aim is to indirectly protect the rest of the population by limiting circulation.

In general, the Hib incidence in Dutch children and adults is higher than in other (Western) countries. Furthermore, since 2012 Hib incidence has increased in children <5 years, despite the vaccination coverage and VE for preventing disease being ≥90 % [9]. This indicates that direct protection is inadequate and indirect protection is limited (1:i). Potential reasons for the increase are investigated, including product changes (from pentavalent to hexavalent Infanrix® in 2011, and to Vaxelis® in 2019), a dose reduction in the routine schedule from 2 to 3–4–11 months to 3–5–11 months in 2020, potential pathogen changes [9], and changes in natural immunity (1,3:ii,iv).

Compared to other countries, the booster at 11 months is offered quite early in the Netherlands [40]. Based on immunological data, a booster given at slightly older age leads to higher antibody concentrations [41]. As prevention of carriage requires higher antibody concentrations than required for prevention of disease [42], delaying the booster may improve direct and indirect protection (2:iii). Given that the Hib incidence is highest among children aged 4–18 months [43], postponing the booster should not be until after 15 months.

Pneumococcus

The main goal of pneumococcal vaccination in the NIP is to prevent invasive pneumococcal disease (IPD) and pneumococcal pneumonia in children <5 years old. The secondary goal is indirect protection of people ≥60 years old against vaccine-serotype disease through herd immunity.

Targeted studies performed in the Netherlands determined an optimal schedule for pneumococcal conjugate vaccines (PCV) [44], resulting in adequate protection against vaccine-serotype disease in targeted and non-targeted age-groups [45] (1:-). The schedule therefore seems optimal (2:-).

In the UK, a reduced schedule (vaccinating at 12 weeks and 12 months; 1 + 1 schedule) is used instead of the 2 + 1 schedule that is used in the Netherlands or the 3 + 1 schedule that is used in several countries [40]. The motivation is that herd immunity likely sufficiently protects infants and a reduced schedule makes room for other vaccinations. In a randomised controlled trial, equivalent or superior immune responses were observed post-booster for the 1 + 1 compared to the 2 + 1 schedule [46]. Those results, together with the virtual disappearance of vaccine-serotypes in the Netherlands, might indicate that the number of doses can be reduced. However, as experience with the reduced schedule is still limited [47], learning from the UK about the direct and indirect effect sizes at longer term is advisable before reducing the Dutch schedule (3:ii).

Pneumococcal vaccination is offered simultaneously with DTaP-IPV-HBV-Hib vaccination, for which delaying the booster may be considered (4:iii). Based on experience in other countries [48,49], we do not expect decreased direct and indirect protection when delaying the booster by several months.

A drawback of pneumococcal vaccination is that non-vaccine-serotype IPD has increased due to serotype replacement in carriage [50] (1,3,5:i). Higher-valent vaccines than the used PCV10 are available and can likely prevent more vaccine-serotype disease [51] (1,3,5:i). However, serotype replacement will likely occur again after implementation of a higher-valent vaccine; the invasive capacity of the replacing serotypes will determine the resulting IPD incidence.

Meningococcus

Meningococcal vaccination aims to prevent invasive meningococcal disease (IMD) in children <5 years old, adolescents, and young adults. The secondary aim is to indirectly protect other age groups through reduction of vaccine-serogroup circulation. MenACWY vaccination of infants and adolescents adequately protects targeted age groups against vaccine-serogroup IMD [52,53] (1:-). Conclusions on the extent of herd immunity cannot be made yet as MenACWY vaccination was introduced only 2 years before IMD incidence reduced as a result of COVID-19 control measures [54]. According to the literature, the possibility of achieving herd immunity by MenACWY vaccination still seems uncertain [53]. However, data from the Netherlands indicate decreased MenACWY circulation [55] and decreased vaccine-serogroup IMD in non-targeted age groups since MenACWY implementation [9,52]. The used vaccination strategy therefore seems appropriate (2:-).

If MenACWY vaccination coverage for 14-year-olds remains high and provides (near) complete herd immunity, indirect protection may sufficiently protect young children. The programme may therefore include too many vaccinations (3:i). Because of the fulminant and unpredictable character of IMD, deciding to remove the infant dose should be based on very thorough considerations.

Eighteen and nineteen year-olds are most commonly colonised and among the main risk groups for IMD [56]. It is thus important that the second dose provides protection up to at least that age. When vaccinating at 15–18 years of age instead of age 12, slightly higher antibody titres are achieved, that possibly wane at a slower rate [57]. Although the current timing seems adequate, programmatic reasons could require the adolescents' dose to be offered at younger age (4:iii). While this would provide protection earlier in life, it would likely be at the expense of the quality and duration of the achieved immunity and thus of (in) direct protection. Adolescent vaccination should therefore not be offered before 12 years of age.

Serogroup B is the dominant cause of IMD in all age groups, but its incidence is low, though increasing [9]. Protein MenB vaccines are available with VEs of >70 % against IMD-B caused by matching strains [53,58]. The NIP may thus include too little to optimally prevent IMD (3:ii). However, MenB vaccines do not protect against carriage and transmission, thereby only providing individual protection. The absence of herd immunity results in assumed unfavourable cost-effectiveness for implementation of MenB vaccination in the NIP [59]. Additionally, their reactogenicity among infants is relatively high. The NITAG will re-evaluate her advice on the use of MenB vaccination in the NIP regularly.

Mumps

The goal of mumps vaccination is to prevent complications from mumps. As little vaccine failure occurs before the booster at age 9 years, primary mumps vaccination appears to provide sufficient direct protection (1:-). In recent years in the Netherlands, mumps mainly occurs among adolescents and young adults with secondary vaccine failure. It often concerns crowding-related outbreaks with mild disease, although orchitis does occur [9,60]. Whether the mumps vaccination strategy is optimal thus depends on how the success of the NIP in protecting young children is weighted against the suboptimal vaccine-derived immunity in adolescents and young adults (2:i,ii,iv). If the strategy of mumps vaccination also includes protection of adolescents, the number of doses and/or the timing is not optimal (2,3,5:ii,iii).

Secondary vaccine failure generally starts 10 years after the booster, likely because of decreased antibody concentration and suboptimal cellular responses [11,61]. Although the booster seems to protect against severe disease and thereby contributes to decreased viral shedding [62], outbreaks still occur. Postponing the booster from 9 to 12–14 years may prolong the period of protection, but scientific support is lacking and it is unknown whether this will be enough to prevent outbreaks (5:iv). Alternatively, targeted vaccination campaigns may provide additional protection for groups susceptible to mumps virus infection during outbreaks [63].

Although the benefits of the mumps vaccination program outweigh the drawback of a shift in mean age of infections, unvaccinated individuals born after introduction of mumps vaccination may present with more severe disease and complications (5:iv).

Measles

Direct protection against measles and maintaining herd immunity are the main aims of measles vaccination in the NIP. Measles elimination from the European region is another goal. The two-dose vaccination programme results in limited primary and secondary vaccine failure, and good herd immunity; the immunogenic vaccine adequately protects most of the population (1,4:i). Recent measles cases in the Netherlands are predominantly individual import cases, but outbreaks in areas with low vaccination coverage can occur (2:ii).

The (import-related) measles cases in regions with clustered orthodox-reformed individuals and in clusters of unvaccinated

individuals with a non-Western migration background pose a risk for outbreaks (2:ii). During outbreaks, children from unvaccinated mothers or children whose maternal antibodies have waned and who are too young to be vaccinated in the NIP (aged 4–6 month up to 14 months) are most at risk (1,4:i). Vaccination as outbreak management can be offered from 6 months of age, but with lower VE and more rapid waning of immunity even after the 14-months dose compared to the regular NIP schedule [64,65]. Early vaccination should therefore only be used in case of high risk of exposure such as during an outbreak. For those opting out of vaccination, a drawback to the NIP is that the age of infection increases. Post-infancy, infections at a later age increase complication frequencies (5:iv).

Around 3 % of children do not respond to the first dose; the booster is needed to reach >99 % seroconversion [11]. The high infectiousness of measles requires such high seroprevalence to reach herd immunity. Therefore, the two doses used in the NIP seem appropriate (3:-). To shorten the period of susceptibility for those with failure to vaccinate or primary vaccine failure, the timing of the second dose could be advanced (4:iii). It is unlikely that such a change will substantially reduce the duration of protection as that mainly depends on the age of primary vaccination [66].

Rubella

The main aim of rubella vaccination is to prevent infections in unborn babies through herd immunity and provide individual protection to future pregnant women, as rubella infections during pregnancy can lead to death and congenital disease in the unborn child. Additionally, rubella elimination is an international goal. Thanks to the highly immunogenic vaccine, the protection of the population is adequate and only sporadic cases occur in the Netherlands, although (infrequent) outbreaks have occurred in orthodox-reformed communities [9] (1,5:i).

Pregnant women who are unvaccinated or with unknown vaccination status, are offered screening for rubella antibodies [67]. If antibodies are absent or too low, vaccination is offered post-partum to protect against rubella during subsequent pregnancies. This strategy of vaccination and screening, leads to very low numbers of congenital rubella syndrome cases (2:-). A screening and vaccination programme targeting unvaccinated young women in villages with low vaccination coverage was evaluated, but appeared unfeasible because of low acceptance [68].

Although profiting from a low rubella incidence, a drawback of the NIP is that those opting out of vaccination lack exposure to rubella and thus do not develop natural immunity. Because of clustering of susceptible individuals among orthodox-reformed communities, outbreaks can be anticipated. This hampers the goal of elimination. In case of an outbreak, unborn children from unvaccinated women are most at risk (1,5:i). Fortunately, there is a trend of increased vaccine acceptance over generations in these communities [69].

Because 99 % of vaccinees seroconvert after the first dose, the second dose may be redundant for population-wide protection and may be omitted as long as the (primary) dose is given after the first year of life (3:ii).

Human papillomavirus (HPV)

The goal of vaccination against HPV is to prevent HPV-related cancer, both in boys and girls. For girls, HPV has been part of the Dutch NIP since 2010, and for boys since 2022. In 2022, the incidence of HPV-related cancers was estimated to be between 0.47/100,000 and 10/100,000, depending on the kind of cancer [70]. The incidence of several HPV-related cancers has been increasing over the period 2000–2015 [71].

HPV-vaccine uptake has been lower than for other NIP vaccines, but has reached ~64 % for birth-cohort 2008 [2]; still too low for the WHO targets on the way to elimination [72]. Catch-up campaigns for boys and girls aged 11 to 18 ran in 2022–23 (2:iii). Also, in 2022, the age of vaccination was lowered from 12–13 to 9–10 years because of its durable effectiveness and to reach more children before sexual debut. The three-dose schedule for persons 15 years and older was reduced to a two-dose schedule [73].

The three-dose (and likely the two-dose) schedule effectively prevents cancer and high-risk cervical lesions [74]. Several studies suggest that a single-dose schedule for children <15 years also protects against persistent HPV infection and may protect against HPV-associated cancer [75,76]. However, a single-dose schedule results in (non-inferiorly) lower antibody titres compared with multiple-dose schedules [76,77]. We therefore concluded that more data on long-term effectiveness of a single-dose schedule is necessary before reducing the Dutch schedule (3:iv).

The possibility that vaccine-targeted HPVs are being replaced by non-vaccine-targeted HPVs cannot be confirmed or ruled out yet. None of the currently available HPV-vaccines induce a response to all oncogenic HPV types, but all include HPV-types 16 and 18 that are responsible for most HPV-related cancers. In the Netherlands, the bivalent vaccine is used, which also induces cross-protection to other oncogenic HPV-types. However, the nonavalent vaccine currently targets most oncogenic HPV-types. Its added value, as well as that of broader vaccines that are in development, should be considered (1:i,ii).

Discussion

The Dutch NIP has been very successful in preventing and/or decreasing the severity of infectious diseases for which vaccines are included in the program [9]. The number and type of vaccines as well as schedules of NIPs vary between countries, depending on, e.g., differences in age-specific disease incidences and existing vaccination visits. NITAGs advice on whether to implement new vaccines. Regular reviewing of the NIP's schedule as a whole gives opportunities for further optimisation of the NIP. We performed such evaluation with a large group of vaccine experts from different fields, by use of fixed criteria. By additionally breaking the schedule down to vaccine-components, this systematic approach enabled identification of possibilities for optimisation for the specific pathogen/vaccine-components first without considering pathogens covered by the shared combination vaccine. Using the criteria for decision-making [4,6,78], NITAGs can advise about potential changes in the schedule by comparing the possibilities for optimisation of the pathogens (in a shared combination vaccine) and weighing these possibilities against the burden of disease caused by the different vaccine-preventable pathogens.

The evaluation showed that protection against some pathogens could be optimised with a change in the age at which vaccines are offered, which would simultaneously decrease redundancies. This includes reducing the number of polio and tetanus doses, increasing the interval between doses for diphtheria, pertussis, tetanus, polio, HBV, and Hib, advancing the second measles vaccination to reduce the number of susceptible individuals at an earlier age, and delaying the second mumps vaccination to reduce (secondary) vaccine failure and prevent outbreaks among adolescents and young adults.

While the schedule for vaccinations against pneumococcal, meningococcal, and HPV infections does not require changes, the multivalency of the vaccines was identified as an issue. Since publishing the evaluation, the NITAG has recommended not to implement MenB vaccination in the NIP at that moment and advised to increase valency of the pneumococcal vaccine; PCV15 is being used for children since autumn 2024.

Combination vaccines provide the advantage of decreasing the number of vaccination moments and injections per vaccination moment. However, combination vaccines make it impossible to define an optimal schedule for every vaccine component or each individual. For example, infants whose mother did not receive an MPV or was HBV-positive during pregnancy, only require additional pertussis or hepatitis B

vaccination, respectively. These vaccines are not provided in the standard NIP, leading to redundancy in these infants' schedule. Otherwise, compromises resulting from combination vaccines are especially present for MMR as the measles and mumps components differ in the optimal age for the second dose. An earlier second vaccination decreases the period of susceptibility to measles for those with primary vaccine failure but might simultaneously reduce immunity against mumps in adolescence. Based on the larger number of lost disability adjusted life years at individual and population level for measles than for mumps, the NITAG advised to give the booster at a younger age [7].

Optimisation of the schedule of vaccine components included in DTaP-IPV-HBV-Hib and the concomitantly given pneumococcal vaccine, does not require compromises as for all included antigens, slightly postponing the 11 months-dose is acceptable or even advantageous. The NITAG therefore advised to move the vaccinations to 12 months of age [7]. To prolong protection against pertussis, decrease side-effects, and remove redundancy in vaccinations against poliomyelitis, the NITAG advised to replace the Tdap-IPV vaccine at 4 years with the Tdap vaccine, which lacks the poliomyelitis component and to increase the age of vaccination to 5–6 years. Consequently, the dt-IPV vaccination will be moved from 9 to 14 years. These advices of the NITAG have been adopted by the Ministry of Health and are planned to be implemented from January 2025 [79].

The goal of the proposed changes in the NIP is to improve the performance of the program, which also depends on the vaccination coverage. The overall coverage of the NIP has slightly decreased over time [2], and increasing the low vaccination coverage in socio-geographically clustered communities remains challenging [80]. Therefore, additional ways should be considered to overcome negative effects of the decreasing vaccination coverage and the presence of clusters with susceptible individuals, including vaccination as management of (measles) outbreaks, screening of pregnant women for rubella (already implemented), and targeted communication strategies [81].

While NIP schedules differ between countries, our evaluation can aid efforts of NITAGs in updating and optimising NIP schedules of their country, including critically evaluating whether all currently offered doses are needed. The continuous generation of scientific data, changes in epidemiology and changes in immunisation practices offer the opportunity to continuously improve NIPs worldwide, which is well worth the effort.

Author contributions

The manuscript is based on the report as referred to by [1], of which the author contributions are as follows: Conceptualization (HH, HvV, NR, HdM); Methodology (HH, HvV, NR, AS, HdM); Project administration (HH, HdM); Investigation (all authors), Visualization (HH); Roles/Writing – original draft (all authors); and Writing – review & editing (all authors). The (additional) contributions of this manuscript are: Conceptualization (AP, AS, HdM); Methodology (AP, AS, HdM); Visualization (AP, AS); Roles/Writing – original draft (AP, AS); and Writing – review & editing (all authors).

CRediT authorship contribution statement

A.J.M. Pluijmaekers: Writing – original draft, Visualization, Methodology, Investigation, Conceptualization, Writing – review & editing. **A. Steens:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Conceptualization. **H. Houweling:** Writing – review & editing, Writing – original draft, Visualization, Project administration, Methodology, Investigation, Conceptualization. **N.Y. Rots:** Writing – review & editing, Writing – original draft, Investigation. **K.S.M. Benschop:** Investigation, Writing – original draft, Writing – review & editing. **R.S. van Binnendijk:** Investigation, Writing – original draft, Writing – review & editing. **R. Bodewes:** Investigation, Writing – original draft, Writing – review & editing. **J.G. M. Brouwer:** Investigation, Writing – original draft, Writing – review & editing. **A. Buisman:** Investigation, Writing – original draft, Writing – review & editing. **E. Duizer:** Investigation, Writing – original draft, Writing – review & editing. **C.A.C.M. van Els:** . **J.M. Hament:** Investigation, Writing – original draft, Writing – review & editing. **G. den Hartog:** Investigation, Writing – original draft, Writing – review & editing. **P. Kaaijk:** Investigation, Writing – original draft, Writing – review & editing. **K. Kerkhof:** Investigation, Writing – original draft, Writing – review & editing. **A.J. King:** Investigation, Writing – original draft, Writing – review & editing. **F.R.M. van der Klis:** Investigation, Writing – original draft, Writing – review & editing. **H. Korthals Altes:** Investigation, Writing – original draft, Writing – review & editing. **N.A. T. van der Maas:** . **D.L. van Meijeren:** Investigation, Writing – original draft, Writing – review & editing. **M. Middeldorp:** Investigation, Writing – original draft, Writing – review & editing. **S.D. Rijnbende-Geraerts:** Investigation, Writing – original draft, Writing – review & editing. **E.A.M. Sanders:** Investigation, Writing – original draft, Writing – review & editing. **I.K. Veldhuijzen:** Investigation, Writing – original draft, Writing – review & editing. **E. Vlaanderen:** Investigation, Writing – original draft, Writing – review & editing. **A.C.G. Voordouw:** Investigation, Writing – original draft, Writing – review & editing. **E.R.A. Vos:** Investigation, Writing – original draft, Writing – review & editing. **J. de Wit:** . **T. Woudenberg:** Investigation, Writing – original draft, Writing – review & editing. **J.A. van Vliet:** Conceptualization, Investigation, Methodology, Writing – original draft, Writing – review & editing. **H.E. de Melker:** Conceptualization, Investigation, Methodology, Project administration, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

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