

**Serogroup C *Neisseria meningitidis* disease epidemiology, seroprevalence, vaccine effectiveness and waning immunity in England from 1998/99-2015/16**

**Keywords**

bacterial meningitis; epidemiology; *Neisseria meningitidis*; surveillance; vaccines and immunisation

**Abstract**

**Background**

The UK was the first country to introduce meningococcal group C (MenC) conjugate vaccination in 1999 and the meningococcal vaccination programme has continued to evolve with further understanding, new vaccines and changing disease epidemiology.

**Methods**

English surveillance data for laboratory-confirmed MenC cases were collated from 1998/99, to 2015/16. Using the screening method, we updated vaccine effectiveness estimates. Typing data and genomes were obtained from the MRF Meningococcus Genome Library and PubMLST *Neisseria* database. Phylogenetic network analysis of MenC cc11 isolates was undertaken. We performed serum bactericidal antibody assays using anonymised sera from 2014 and compared results to seroprevalence data from 1996-1999, 2000-2004 and 2009.

**Results**

MenC cases fell from 883 in 1998/99 (1.81/100,000 population), to 42 cases (0.08/100,000 population) in 2015/16. A trend for lower vaccine effectiveness with increasing time since vaccination was observed after infant immunisation (P=0.009) and a single dose at 1-4 years (P=0.03). After vaccination at 5-18 years, high effectiveness was sustained for ≥8 years; 95.0% (95% CI, 76.0 to 99.5%). Only 25% (75/299) children aged 1-14 years were seroprotected against MenC disease in 2014. Recent MenC case isolates were diverse, but mostly represented two diversifying cc11 strains.

**Conclusion**

High quality surveillance has furthered understanding of MenC vaccines and informed revisions to schedules to maximise population benefit at minimal cost. The UK programme continues to ensure high direct and indirect protection despite low levels of seroprotection in some age groups but certain high risk groups persist. High-resolution characterisation supports ongoing surveillance of distinct MenC cc11 lineages.

**Introduction**

*Neisseria meningitidis* is a major cause of meningitis and septicaemia worldwide. Efforts to control meningococcal disease have been aimed at the development of effective vaccines and subsequent implementation in appropriate immunisation schedules. Twelve different meningococcal serogroups are recognised; while serogroup B (MenB) is currently responsible for most cases of invasive meningococcal disease (IMD) in Europe, many countries, including the UK, experienced large outbreaks of serogroup C (MenC) disease in the mid-1990’s, due mainly to the ST-11 clonal complex (cc11) [1]. In 1999, the UK became the first country to introduce the MenC conjugate (MCC) vaccine in a phased national campaign targeting all <18 year-olds over a 12-month period, alongside a routine three-dose infant programme [2]. Vaccine eligibility was later extended up to 24 years of age, although this age-group was not actively called for vaccination. Routine use of MCC vaccine in many other European countries followed.

Comprehensive national surveillance was initiated concurrently to monitor the impact of the UK programme because the MCC vaccines were licensed on immunogenicity studies alone without direct evidence of clinical efficacy. MCC vaccination was associated with rapid and sustained declines in MenC disease across all age-groups through direct and indirect (herd/population) protection [2, 3, 4]. Invasive disease is rare following nasopharyngeal acquisition where the meningococcus can persist for several months before it is cleared; this asymptomatic carriage – especially in older teenagers – is an important reservoir for infection, onward transmission to susceptible individuals and immunity. In the UK there was a 66% reduction in MenC carriage among 15-19 year-olds within one year of MCC vaccine implementation; this reduction was key to establishing indirect protection across the population [5].

The UK MCC immunisation programme has evolved over time (Box 1) and from 2013, has included an adolescent MCC vaccine programme to extend direct protection in teenagers and maintain herd protection in the wider population. In 2015 this was replaced with MenACWY conjugate vaccine programme to combat a national MenW outbreak, as well as a multi-component, protein-based vaccine against MenB in the infant immunisation schedule [6]. In July 2016, the infant MCC dose was removed because MenC cases were extremely rare in this age-group and population protection was likely to be maintained through the adolescent MenACWY programme.

Given resource limitations it is important that vaccination programmes are optimally delivered to ensure maximal population benefit. Here, we evaluate the long-term impact of a national MCC vaccination programme in England on (i) MenC epidemiology, (ii) the clinical characteristics of confirmed MenC cases, (iii) MCC vaccine effectiveness (VE), (iv) characterisation of MenC isolates from invasive cases and (v) population immunity through national serosurvey updating previous studies [7,8,9].

**Methods**

**National epidemiology**

Public Health England (PHE) conducts enhanced national surveillance of IMD in England. The PHE Meningococcal Reference Unit (MRU) provides a national service for confirming, grouping and characterising invasive meningococcal isolates [10]. The MRU also provides free national PCR-testing of clinical samples from patients with suspected IMD.; Diagnostic laboratories are required by law to notify PHE when they identify *Neisseria meningitidis* and samples are requested to be sent to the MRU for confirmation and characterisation. PHE routinely reconcile laboratory-confirmed cases to generate a national dataset [11]and follows- up each case for demographic data, vaccination history, clinical presentation and outcomes through Health Protection Teams (HPTs), general practitioners and, for younger cases, hospital clinicians. Details documented on HPZone, (a web-based software for public health management of infectious diseases used by HPTs throughout England), were also accessed by PHE to obtain additional information on cases since 2010.

**Vaccine effectiveness**

Using the national dataset MCC VE was calculated using the screening method [12] for confirmed MenC cases among MCC-eligible individuals (born since 01/09/1981) in England between 01/01/2000 and 30/06/2016. VE was estimated according to time since vaccination (or, if unvaccinated, since the age at last scheduled dose); analysis included unvaccinated children, those who had completed the recommended primary immunisation course for their birth cohort (three doses for <1 year-olds before September 2006), or had received one dose after their first birthday at any age. Effectiveness of the primary plus booster dose was based on cases who had received $\geq $1 primary MCC dose followed by the 12-month Hib/MCC booster. The following formula was used: VE = 1−[PCV(1−PPV)]/[(1−PCV)PPV], where PCV is the proportion of vaccinated MenC cases and PPV is the proportion of vaccinated population (i.e., vaccine coverage, matched to each case based on their age and birth cohort and then averaged). Annual national vaccine coverage by 12 months of age (from April 2001) and by 24 months of age (from April 2002) was used for the latter [13].

Data extracted in May 2016 from The Health Improvement Network (THIN) database (<http://www.inps.co.uk/vision/thin/about-us>) for children born from 1999 to May 2015 was used to estimate partial vaccination proportions for each of the routine schedules (3+0, 2+1,1+1) by 12 months and 24 months of age. These estimates of partial vaccination were used to adjust the national coverage estimates to give coverage in those who receive either no vaccination or the full the schedule. For example, it was estimated that in the three-dose primary cohort, 5.5% received one or two doses by 12 months, so national coverage of 90% for three doses would be adjusted to (90\*100)/(100-5.5)=95.2%, once partial vaccination is excluded.

**Molecular characterisation**

Typing data and genomes were obtained from the PubMLST *Neisseria* database and Meningitis Research Foundation Meningococcus Genome Library (MGL), to which all MRU isolates from the national dataset have been referred since July 2010 [14,15]. A recent phylogenetic network analysis of the known population structure of MenC-associated cc11 sublineages was re-annotated in the context of the current study since cc11 represented the majority of recent invasive MenC isolates in England [16]. Briefly, all available global cc11 genomes, including 121/122 invasive MenC isolates from England (2010/11 to 2015/16), and excluding serogroup W-associated lineage 11.1 sublineages (final n=898 globally; accessed 07/10/16), and two non-cc11 reference genomes (IDs 27778 and 29645; ccs 41/44 and 8, respectively), underwent core genome comparisons (1546 loci) using the PubMLST genome comparator tool. The resulting distance matrices were visualised using SplitsTree4. The invasive MenC cc11 isolates collected in England during 2010/11 to 2015/16 (inclusive) were highlighted [17].

**Serosurvey**

Serum samples collected in 2014 were obtained from the PHE Seroepidemiology Unit; a depository of anonymised residual sera from routine diagnostic testing at participating laboratories. Known immunocompromised individuals are excluded from the collection. The age, sex and year of collection were known for individual samples: immunisation status was not known [18].

Serum bactericidal antibody (SBA) assays were performed against the serogroup C target strain, C11 (phenotype C:16:P1.7-1,1) as previously described [19]. The complement source used in the SBA was pooled serum from 3-4 week old rabbits (Pel Freez Biologicals, WI USA). Titres were expressed as the reciprocal serum dilutions yielding ≥ 50% killing after 60 min. The lower limit of detection was a titre of 4. Titres of <4 were assigned a value of two for geometric mean titre (GMT) analysis. Titres of ≥8 were considered protective against MenC disease [20].

Approximately 100 samples were selected from each age-band to fit with different vaccine schedules since MCC introduction and to allow comparison with previous studies. This sample size was selected to achieve reasonable precision around the 95% confidence intervals (CIs) for proportions with SBA titres ≥8 and GMTs within the age-group of interest.

Since MCC vaccine coverage has been consistently high, the age of the serum donor was used to estimate the eligible vaccine schedule for comparison of protection between schedules and over time, using historical data from three previously published similarly designed surveys using sera collected from the same Seroepidemiology Unit and tested using the same methodology in the same PHE laboratory during 1996-1999 [7], 2000-2004 [8] and 2009 [9].

**Results**

**Epidemiology**

MenC cases in England fell rapidly from 883 in 1998/99 (pre-vaccination year, incidence 1.81/100,000) to a low of 13 cases in 2008/09, continuing at low levels (17-33 cases annually) during 2009/10-2014/15. In 2015/16, there were 42 cases (0.08/100,000), similar to disease levels last observed in 2004/05 (Figure 1). Over the last decade overall age distribution has been relatively constant (Figure 1). However, the proportion of cases among 5-14 years increased from 12% between 2006/07-2010/11 (0.04/100,000) to 17% between 2011/12-2015/16 (0.09/100,000), while the proportion of cases among 1-4 year-olds declined from 11% (0.09/100,000) to 4% (0.05/100,000) over the same period. Cases in those aged 45 years and over (who are unvaccinated) were 86% lower in 2015/16 (n=16) than 1998/99 (n=111) consistent with a sustained herd protection effect.

Between 2011/12 and 2015/16, 160 MenC cases were confirmed and 18 died (CFR, 11%). The London region, where 16% of the English population resides (8.7 of 54.8 million) accounted for 41% of cases (n=66). Overall, 82 cases were female and 78 male but the sex distribution differed by age with a preponderance of males aged 25-44 years (30/47) and of older female cases aged ≥45 years (35/53). Thirty-two cases (20%) had a history of recent travel. Seventeen cases were born outside the UK and were more likely to have recently travelled (15/17) than UK-born individuals (17/143).

Eleven of 160 cases (7%) were living in shared accommodation (three university students, four in care homes or assisted living, four in house share or hostel accommodation). There were six cases in men who have sex with men (MSM) and eight individuals reported using recreational drugs, were injecting drug users or had alcohol dependency. Nineteen cases (12%) had underlying co-morbidities; heart condition (n=3), diabetes (n=2), HIV (n=6), immunosuppression (2 on psoriasis treatment, one with chronic lymphocytic leukaemia, one post liver transplant), chronic respiratory condition (n=3), liver disease (n=3). There were three clusters of two cases each in primary schools nationally in 2015; all six children were fully-vaccinated (two-dose primary course with booster).

**Vaccine effectiveness**

Between 1 January 2000 and 30 June 2016, there were 316 MenC cases in vaccine-eligible individuals, of whom 119 had been fully-vaccinated according to their recommended schedule (Table 1). Estimated VE within 12 months of immunisation at all targeted ages (including infants) was high. Following routine infant vaccination or a single dose administered to cohorts aged one to four years when the catch-up programme began, a trend for lower VE with increasing time since vaccination was observed (P=0.009 and P=0.03 respectively) (Table 1). In school-aged cohorts (aged 5-18 years when immunised), high VE was sustained over time, remaining at 95.0% (95% CI, 76.0 to 99.5%) $\geq $8 years after vaccination. Of the 26 cases eligible for the Hib/MenC booster, 25 were vaccinated, with matched coverage of 94.6%; VE was -43% but with wide confidence intervals (95% CI -5759 to 77%). This calculation is very sensitive to the number of unvaccinated cases; for example, the addition of just two unvaccinated cases would change this estimate to 52%.

**Molecular characterisation**

During 2010/11-2015/16, there were 182 laboratory confirmed MenC cases in England’s national dataset, of which 122 were culture-confirmed. Molecular characterisation was available for 121 isolates and most (89/121, 73.6%) belonged to the ST-11 complex (cc11), ranging from 4 of 12 in 2010/11) to 27 of 30 in 2015/16). Other clonal complexes included cc103 (n=9), cc269 (n=6), cc-unassigned (n=5), cc32 (n=3), cc41/44 (n=3), cc174 (n=2) and a single isolate each for cc116, cc23, cc334 and cc60 (Figure 2). The population structure of cc11 (minus the serogroup W-associated lineage 11.1 sublineages) [16] comprised two main lineages, lineage 11.1 (corresponding to ET-37; n=245; 6 MenB, 229 MenC, 1 MenY and 9 serogroup unspecified) and lineage 11.2 (corresponding to ET-15; n=649; 77 MenB, 536 MenC, 3 MenW and 33 non-groupable/serogroup unspecified) (Figure 3a).

The English cc11 case isolates from 2010/11 to 2015/16 belonged to both lineage 11.1 (n=32; 36.0%) and lineage 11.2 (n=57; 64.0%), where they mainly belonged to several closely-related clusters (Figure 3a). The predominant PorA subtypes were P1.5,2 (93.8%) and P1.5-1,10-8 (96.5%), respectively. Since 2010/11, the number of lineage 11.1-related cases increased from one to 10 per year, while the lineage 11.2-related cases varied between three (2010/11) and 17 (2015/16) (Figures 3b and 3c). Isolates from vaccine-failure cases were well distributed among the overall English MenC cc11 population (not shown).

**Serosurvey**

Results were available for 993 samples collected in 2014 and 323 (33%; 95% CI, 30.1 to 35.9) had SBA titres ≥8. The proportion of individuals achieving the seroprotective threshold was remarkably similar across the age groups in 2014 compared to 2009 (Figure 4). In contrast, much higher proportions of 5-19 year-olds were seroprotected during 2000-04, the period immediately after the 1999/2000 national catch-up for 0-18 year-olds. This cohort is now older and responsible for the secondary peak of seroprotection among 15-34 year-olds in subsequent serosurveys. Notably, only 38% of 15-19 year-olds achieved the seroprotective threshold in 2014 compared to 56% in 2009. Only 25% (75/299) children aged 1-14 years were seroprotected against MenC in 2014.

The 14/15 year-olds and 16 year-olds were separated in 2014 because they received different primary vaccination (Table 2) and to maintain consistency with the 2009 survey. Analysis by birth cohort and eligible vaccine schedule suggested higher GMT (10.6, 95% CI 4 to 29 vs. 3.7, 95% CI 2 to 6) and proportions with SBA titres >8 (28.2%, 95% CI 15 to 44 vs. 17.0%, 95% CI 8 to 30) among 14-15 year-olds (the cohort eligible for the adolescent booster) in 2014 compared to 2009 (Table 2). In the younger age-groups, GMTs and proportion protected were generally lower in 2014 compared to 2009 (Table 2).

**Discussion**

**Epidemiology**

MenC disease in England remains at very low levels with an incidence of 0.08/100,000 in 2015/16, an overall reduction of 95.6% compared to 1998/99 before MCC vaccination was introduced. Nearly a third of cases are currently diagnosed in 25-44 year-old adults, many with clinical, social and travel-related risk factors. Case fatality remains unacceptably high. Updated VE estimates indicate a rapid decline in protection after one year following routine infant immunisation, but remain high for children immunised at school age (5-18 year-olds) up to at least eight years after vaccination.

The low MenC disease incidence is reassuring, with no cases reported among at-risk individuals, currently defined as those with asplenia, splenic dysfunction or complement deficiency. Those born outside the UK (who are less likely to be immunised with MCC, even if eligible on entry), recently travelled and/or socially mixing with these populations accounted for a quarter of all cases, while a significant proportion of the other cases were living in shared or supported accommodation; a known risk factor for invasive meningococcal disease [21]. We and others have recently reported an increased risk of IMD in HIV-positive individuals [22], even after appropriate antiretroviral therapy, and, over the past five years, six HIV-positive individuals were identified among 160 MenC cases in England. Outbreaks of MenC disease in MSM populations have been also reported in North America and Europe; six cases were identified in England over the past five years, all in the 25-44 year age-group, including two who were non-UK born and had recently travelled abroad. Whole genome sequencing previously showed that MenC case isolates among MSMs in England, whilst all belonging to lineage 11.2, were interspersed among sporadic community case isolates and did not form a discrete cluster [23].

**Molecular characterisation**

Recent MenC cases in England were caused by diverse meningococcal strains, representing at least ten different clonal complexes over the past six years. Most cases, however, were caused by two diversifying cc11 strains, one each from the two recently-resolved major cc11 lineages (lineages 11.1 and 11.2) [23, 24]. Our findings warrant continued close monitoring since lineage 11.1 cases have increased steadily over the past six years, whilst 2015/16 also saw the greatest number of lineage 11.2 cases. In addition to high case fatality rates for cc11 in general, the presence of lineage 11.2 isolates is concerning for several reasons. Evidence of frequent MenB to MenC capsule switching is coupled with poor potential coverage by, and the ability to escape from, several existing and experimental MenB vaccines [16]. Furthermore, distinct lineage 11.2 populations have independently acquired traits that may facilitate urogenital colonisation [25, 26]. The acquisition of intact *aniA* alleles encoding nitrite reductase may enable survival in microanaerobic environments and has been associated with outbreaks of invasive disease among MSM in the USA and Europe [26, 27, 28], and urethritis among heterosexual males in the USA [25,26]. The urethritis-associated strain has also lost its ability to express a capsule, a further gonococcal trait that may facilitate adherence to the urogenital mucosa.

**Serosurvey**

Seroprevalence studies have proven valuable in improving our understanding of population immunity, inform mathematical modelling and can complement disease surveillance to help inform national vaccine policy [7, 8, 9].The 2014 serosurvey confirmed the rapid decline in immunity after infant and toddler immunisation, which was also observed with the 2009 serosurvey, as well as the low proportion of teenagers protected against MenC disease around the time when the adolescent programme was introduced. Similar trends have been reported in the Netherlands, where a large catch-up campaign targeting 1-19 year-olds in 2002 was followed by routine childhood immunisation at 14 months of age only. Here a recent serosurvey found only 19% of 10 year-olds were protected nine years after a single MCC dose at 14 months [29]. The successful control of MenC disease in the UK is attributed to the large catch-up campaign in 1999/2000. Teenagers and young adults have the highest nasopharyngeal meningococcal carriage rates and are considered the main source of spread. MCC vaccines not only protect against invasive disease but also against nasopharyngeal acquisition, thereby inducing herd protection across all age-groups [5]. The current cohort of younger children with poor seroprotection is most likely protected against disease because of this indirect protection.

Most adolescents in 2014 will have received a three-dose infant schedule without a booster. The low proportion of teenagers achieving protective antibody thresholds in the 2014 serosurvey indicates poor long-term direct protection in the cohort that was only immunised in infancy that potentially threatened ongoing herd protection across the population. This observation, predicted after the 2009 serosurvey, helped support the inclusion of MCC in the adolescent programme in 2013 with the aim of providing high antibody concentrations throughout the peak years of carriage [6]. The 2014 serosurvey is already demonstrating higher MCC antibodies among 14-16 year-olds compared to the same age group in the previous serosurvey. The emergency adolescent MenACWY programme in 2015 was implemented to provide direct and population protection, not only against MenC but also against the three other serogroups, particularly the emergent hypervirulent MenW strain also belonging to cc11 that was responsible for a quarter of all IMD cases across the UK by 2014/15 [6].

**Implications for other countries**

In Europe, MenC disease incidence is currently low (<1/100,000) in countries with and without routine MCC vaccination [4]. Disease in infants remains rare and, in countries with routine MCC immunisation, most cases occur in adults, with a median age of 41 years compared to 22 in countries without MCC vaccination programmes. The recent increase in MenC cases in France highlights the importance of maintaining high vaccine coverage, especially in adolescents, in order to sustain long-term direct and indirect disease control [30]. A number of countries across Africa, Latin America and elsewhere are also experiencing high MenC disease activity [31, 32]; travellers to such countries, including residents visiting family and friends in their home countries, should be appropriately immunised, advised to avoid high-risk behaviours, remain vigilant of symptoms and signs of meningococcal disease and seek immediate medical help if concerned whilst abroad and when returning to their home countries.

**Strengths and limitations**

The strength of this study is the consistently high quality of the national surveillance programme with high case ascertainment [11], and active follow-up of cases since 1998/99. This has allowed us to monitor VE in different cohorts and over time. Our meningococcal surveillance is complemented with clinical trials to assess different schedules and serosurveys to monitor population susceptibility. Together, these results have allowed us to adapt the national immunisation programme to provide maximal long-term protection in the most cost-efficient manner. Using the same methodology allows us to monitor population effects over time. A limitation of the serosurvey, however, is that we have no information on the vaccination status of the serum donors or their clinical state. The large numbers of samples tested, however, along with the consistently high vaccine coverage nationally allowed us to analyse the results by birth-cohorts

**Conclusions**

Taken together, our results confirm rapid waning of immunity following routine infant immunisation, even with a 12-month booster which was introduced in 2006. Currently, most toddlers and older children in England are not seroprotected against MenC disease and are dependent on the indirect protection offered through reduced carriage in older teenagers. It is, therefore, reassuring that there is still evidence of herd protection in adults 17 years after mass vaccination of children in 1999. Immunisation of teenagers appears to be key to continued population impact but also for direct protection at an age when behaviour leads to greater exposure, carriage and invasive disease. We have demonstrated high short-term effectiveness of MCC vaccines in infants and pre-school children and the long-term effectiveness of MCC vaccines given to school-aged children and adolescents. These findings have led to several revisions of the UK immunisation schedule to maximise direct and indirect protection. The recent change to emergency MenACWY vaccination for teenagers was brought in to provide more rapid population control for the national MenW outbreak, but should also allow more rapid direct and population control for MenC and MenY disease.

Continued epidemiological and microbiological surveillance will be critical to monitor current programmes which now include newer sub-capsular protein-based vaccines against MenB disease in infants. MenC disease continues to be rare but detailed case-based follow-up has identified certain groups that remain at higher risk for MenC disease despite containment within the wider population, these groups may benefit from targeted vaccination. Stochastic meningococcal outbreaks globally need to be carefully monitored, as well as the recent MenC outbreaks amongst MSM. High-resolution characterisation is critical to monitor circulating strains and detect known and unknown emerging threats.

**Box 1: Summary of the changing UK meningococcal immunisation schedule**

1999: Routine infant vaccination at 2, 3, 4 months of age MenC vaccine

 Catch-up of children aged 5 months to 18 years MenC vaccine

2006 Routine infant vaccination at 3 and 4 months of age MenC vaccine

Booster at 12 months of age MenC/Hib vaccine

2013 Routine infant vaccination at 3 months of age MenC vaccine

 Booster at 12 months of age MenC/Hib vaccine

 Booster at 13-15 years of age MenC vaccine

2015 Routine infant immunisation at 2 and 4 months of age MenB vaccine

 Routine infant immunisation at 3 months of age MenC vaccine

 Booster at 12 months of age MenB vaccine

 Primary dose (of MenC) at 12 months of age MenC/Hib vaccine

 Routine teenage dose at 13-15 years of age MenACWY vaccine

 Catch-up of teenagers aged 15-18 years MenACWY vaccine\*

2016 Routine infant immunisation at 2 and 4 months of age MenB vaccine

 Booster at 12 months of age MenB vaccine

 Primary dose (of MenC) at 12 months of age MenC/Hib vaccine

 Routine teenage dose at 13-15 years of age MenACWY vaccine

**\*completed in 2017**

** Figure 1:** Incidence rate of group C meningococcal disease by epidemiological year 1998/99 to 2015/16, England.

**Inset graph:** Distribution of laboratory confirmed cases of group C meningococcal disease by age group over the most recent 10 epidemiological years, England only 2006/07 to 2015/16.

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**Figure 2.** Clonal complex distribution among meningococcal serogroup C case isolates in England, 2010/11 to 2015/16.

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**Figure 4.** Seroprotection against serogroup C meningococci measured by proportions with serum bactericidal antibody (SBA) titres of ≥8. Comparison of levels in 2014 with the previous surveys conducted prior to MCC vaccine introduction in 1996-1999 and following introduction in 2000-2004 and 2009.

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