**Risk of invasive bacterial infections by week of age in infants: prospective national surveillance, England, 2010-2017**

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**What is already known on this topic**

* Young infants have the highest risk of invasive bacterial infections (IBI)
* The MenB vaccine, 4CMenB, is associated with high rates of fever in infants
* It is difficult to differentiate post-vaccination fever from underlying infection in young infants

**What this study adds**

* In infants, the incidence of IBI is highest in the first week of life and then falls rapidly
* In 2016/17, compared to the first week of life, weekly IBI incidence was 92% lower at 8 weeks and 96% lower at 16 weeks of age
* Infants have a very low risk of IBI by the time they are eligible for their routine immunisations

**Abstract**

**Objective:** to estimate the incidence of laboratory-confirmed, invasive bacterial infections (IBI) by week of age in infants over a seven-year period.

**Design**: retrospective analysis of national surveillance data for England

**Setting**: National Health Service Hospitals in England

**Patients:** Infants aged <1 year who were hospitalised with IBI

**Main outcome measures:** IBI incidence by week of age, incidence rate ratio at 8, 12 and 16 weeks compared to the first week of life; main pathogens responsible for IBI

**Results:** There were 22,075 IBI episodes between 2010/11 and 2016/17. The lowest annual cases were in 2011/12 (n=2,799; incidence, 412/100,000 population), increasing year-on-year to 3,698 cases in 2016/17 (incidence, 552/100,000 population). The incidence was highest in the first week of life, and then declined rapidly. In 2016/17, compared to the first week of life, weekly IBI incidence was 92% lower at 8 weeks (IRR, 0.08; 95% CI, 0.06-0.10) and 96% lower at 16 weeks of age (IRR, 0.04; 95% CI, 0.03-0.06). In 2016/17, *E. coli* was the single most important pathogen (n=592, 16.0%), followed by Group B Streptococci (n=493, 13.3%), *Staphylococcus aureus* (n=400, 10.8%) and *Enterococci* (n=304, 8.2%). The other pathogens were individually responsible for <5% of total cases. There were differences in age distribution of the pathogens with increasing age.

**Conclusions:** IBI incidence declines rapidly after the first week of life, such that infants have a very low risk of IBI by the time they are eligible for their routine immunisations at 8 weeks of age.

**Introduction**

Infections remain a major cause of morbidity and mortality in infants worldwide. Immunisation against the major pathogens, especially those responsible for bacterial meningitis, has had a major impact in reducing disease burden in this vulnerable age group, especially in industrialised countries where vaccines are readily available and vaccine uptake is high. A consequence of successful national immunisation programmes is that the epidemiology of childhood infectious diseases has changed, with near elimination of many vaccine-preventable diseases, especially the major pathogens responsible for bacterial meningitis.1

In industrialised countries with established national immunisation programmes, the burden of childhood infections is highest in the first few weeks after birth, especially during the period immediately after birth (early-onset disease, EOD). After this time, the risk of serious infections falls rapidly, especially after the first month of life. Yet, the number of infants hospitalized in the UK has been increasing progressively over the past decade.2 Identifying the small number of infants with serious invasive bacterial infections (IBI) among the many who present to the Emergency Department (ED) with self-limiting viral infections remains a major challenge for frontline clinicians, especially given that the clinical presentation is often non-specific and disease progression can be very rapid in this age group.3

In the UK, this has become even more challenging following the introduction of the novel, multicomponent, protein-based meningococcal B vaccine (4CMenB, Bexsero®; GSK Biologicals, Belgium) into the national infant immunisation programme since September 2015.4 When administered with other routine immunisations, 4CMenB is associated with high rates of fever and other vaccine-related adverse reactions.4 Despite recommendations for administration of prophylactic paracetamol around the time of vaccination, a small but significant increase in primary care and ED attendances for infants with fever has been reported since the introduction of 4CMenB vaccination.5,6

Understanding the *a priori* risk of IBI in febrile infants is important so that clinicians can undertake risk-appropriate decisions regarding, investigations, empiric antibiotics and admission to hospital for observation or treatment. In the UK, the National Institute of Health and Care Excellence (NICE) has published guidelines to improve the recognition, assessment and immediate treatment of febrile illnesses with no obvious cause in children under 5 years of age.7 These guidelines were last amended on August 2017. Currently, the guidelines state that children younger than 3 months with a temperature of 38°C or higher are in a high-risk group for serious illness and recommend extensive investigations with a low threshold for initiating empiric intravenous antibiotics. We speculated that the highest risk IBI in infants was in the first month of the life and that this risk declined very rapidly by the time infants became eligible for their routine immunisations. We, therefore, used national surveillance data for England to estimate the incidence of laboratory-confirmed IBI in infants by week of age over a seven-year period. We hope that our findings will help inform national policy, especially for infants presenting to hospital during the post-immunisation period.

**METHODS**

Participating NHS laboratories in England electronically report microbiology results and demographic data to Public Health England’s (PHE) Second Generation Surveillance System (SGSS), which replaced its predecessor LabBase2 in December 2014. Approximately 98% of hospital microbiology laboratories in England (125 in 2016/17) report to PHE through SGSS (https://www.gov.uk/government/publications/english-surveillance-programme-antimicrobial-utilisation-and-resistance-espaur-report). In England, blood and cerebrospinal fluid cultures (CSF) are almost always performed in the hospital setting, either in the emergency department or among in-patients. Microbiology and demographic data for all positive bacterial blood and CSF cultures from children aged <1 year at the time of the positive specimen date in England were extracted from SGSS using the Communicable Disease (CDR) module between 2010/11 and 2016/17. Multiple specimen samples were de-duplicated where the same pathogen was isolated from the patient within 14 days.8

Coagulase-negative Staphylococci, *Micrococcus* spp., *Propionibacterium* spp., diphtheroids, *Streptococcus viridans* and any other bacteria usually considered contaminants in healthy patients were excluded from the data extract. Data were managed and analysed in STATA version 13.1 (StataCorp, College Station, Tx). Mid-year population estimates and live birth data for England were sourced from the Office of National Statistics (<https://www.ons.gov.uk/>). Annual incidence was calculated for each financial year (April to the following March) by dividing the number of infants (aged <1 year) with IBI by the total number of infants in England for that year. For each financial year, the incidence by week of age was calculated by dividing the number of cases with IBI for each week of age with the estimated number of infants in England during the same week of age (i.e. total number of infants in England in that year divided by 52). The incidence rate ratio with 95% confidence intervals was calculated by dividing the incidence in the week of interest by the incidence in the first week of life.

**RESULTS**

In England, there were 22,075 laboratory-confirmed IBIs in infants (aged <1 year) between 2010/11 and 2016/17 (Table 1). The lowest annual number of cases was in 2011/12 (n=2,799; incidence, 412/100,000 infants), increasing year-on-year thereafter to 3,698 cases in 2016/17 (incidence, 552/100,000 infants). Neonates (<1 month-old) accounted for 49.0% (n=10,826/22,075) of all cases, and young infants (<3 months old) for 70.9% (n=15,642/22,075).

When assessed by week of age, the incidence was highest in the first week of life, and then declined rapidly (**Figure 1**). In 2016/17, compared to the first week of life (172/100,000 infants), weekly IBI incidence was 89% lower at 4 weeks (19/100,000 infants; IRR, 0.11; 95% CI, 0.09-0.14), 92% lower at 8 weeks (14/100,000 infants; IRR, 0.08; 95% CI, 0.06-0.10), and 96% lower at 16 weeks of age (7/100,000 infants; IRR, 0.04; 95% CI, 0.03-0.06).

**Bacterial pathogens**

In 2016/17, *Escherichia coli* was the single most important pathogen responsible for IBI in infants (n=592, 16.0%), followed by Group B Streptococci (GBS; n=493, 13.3%), *Staphylococcus aureus* (n=400, 10.8%) and *Enterococcus* spp. (n=304, 8.2%). The other pathogens were individually responsible for <5% of total cases. There were differences in age distribution by pathogen (Figure 2). For nearly all pathogens, more than 50% of cases occurred in the first 3 month of life, especially GBS (472/493 cases, 96%) and *E. coli* (466/592 cases, 79%), with the notable exception of *Streptococcus pneumoniae,* where half the infections (61/122 cases) occurred in the second half of the first year of life. All seven IBI caused by *Listeria* spp. occurred in the first week of life.

**DISCUSSION**

Our results demonstrate that the incidence of laboratory-confirmed IBIs in neonates, young infants and older infants has been increasing for the past six years. Almost half of all IBIs occur in the first month of life, mainly in the first week of life. Analysis by week of age shows a rapid decline in IBI incidence after birth. Infections in early life are predominated by GBS and *E. coli*, which become less prevalent with increasing age.

The electronic SGSS platform is used by NHS hospital laboratories to notify PHE of significant infections across England. This is an automated process that facilitates rapid surveillance of infectious diseases nationally. Although reporting to SGSS is voluntary, comparison with other mandatory reporting systems for specific pathogens indicates very high reporting rates.9 Our analysis involved infants who had positive blood/CSF cultures taken for suspected IBI in the hospital setting. Given the limited sensitivity of bacterial cultures and because the analysis did not include clinically diagnosed infections or non-invasive infections such as pneumonia and urinary tract infections, the true IBI incidence in infants will be higher.

The SGSS surveillance is limited by lack of clinical data accompanying the notifications. Although some pathogens, such as meningococci or GBS, are invariably associated with serious illness, others such as *S. aureus* may possibly be contaminants and, therefore, need to be evaluated in the context of the patient’s clinical condition. Additionally, the estimated incidence by week of age included both community-acquired infections in infants presenting to the ED and nosocomial infections in hospitalised infants, including recently-born infants with early onset IBI and premature infants in the neonatal intensive care unit. Ideally, we would have liked to estimate IBI risk among infants presenting to ED with fever by week of age, but we were unable to obtain the required denominator data for this analysis. It is also important to note that clinicians are likely to have lower thresholds for investigating and treating younger infants for suspected sepsis; this could possibly partly explain the lower IBI rates in older infants but unlikely to influence the rapid declines observed in younger infants, particularly in the first month of life.

The strength of SGSS surveillance lies in the near-real time prospective national data collection across England. While the true burden of infection may be underestimated, the consistent methodology over the years allows monitoring of disease trends over time as well as the age distribution of cases and the pathogens responsible for infection. The year-on-year increase in annual IBI incidence over the past five years is noteworthy and, if confirmed in other studies, merits further investigation. Remarkably, there are very limited published data on the risk of IBI by week of age in infants, with most studies focusing on early onset infections in the first week of life, neonatal infections or the first 3 months of life. Additionally, many of the studies were published prior to the implementation of the childhood immunisation programmes specifically targeting the major pathogens causing IBI in this age group.10 Moreover, IBI risk will change over time as immunisation programmes evolve and new prevention strategies are implemented. Thus, understanding the *a priori* risk of IBI when assessing infants at different ages is important when making decisions about undertaking invasive investigations, considering hospitalisation and initiating empiric antibiotic therapy.

Among the older publications, a US study analysed data from 3,066 consecutive infants aged ≤3 months with fever (38°C or higher) assessed by any of 573 practitioners from the Pediatric Research in Office Settings (PROS) network during 1995-98. The authors reported a 5.56-fold (95% CI, 2.50-12.36; P<.001) and 3.03-fold (95% CI, 1.35-6.81; P=0.007) increased risk of bacteraemia/meningitis in infants aged ≤30 days and 31-60 days, respectively, compared to older infants.11 The absolute rates of bacteraemia/meningitis were 4.1%, 1.9% and 0.7% in these three age-groups, respectively.

In a more recent retrospective US cohort study of 35,070 emergency department visits among infants aged <90 days with a diagnosis code of fever during 2011-13, the rate of significant bacterial infection (UTI or pyelonephritis, bacteraemia or sepsis, bacterial meningitis, pneumonia, or bacterial enteritis) was 11.15% in ≤28 day-olds, 7.5% among 29-56 day-olds and 7.7% among 57-89 day-olds.12 Most infants (n=1,854, 5.3%) were diagnosed with UTI, 830 (2.4%) with bacteraemia or sepsis, and 122 (0.3%) with meningitis. Analysis by week of age revealed that cases increased from birth and peaked at 3 weeks of age, before declining until 6 weeks and remaining stable thereafter. Our recent audit of 1,097 febrile children attending a large tertiary ED in London during 2014-2015 found only two (0.2%) cases with significant bacteraemia,13 which is similar to the bacteraemia rate of 0.4% reported among >15,000 febrile children attending the ED in Australia.14

In the current analysis, the highest risk of IBI among UK infants is in the first week of life, which then declines rapidly, being 89% lower by 4 weeks of age and 92% lower by 8 weeks of age, when they become eligible for their routine primary immunisations. In the UK, the National Institute of Health and Care Excellence (NICE) has published guidelines to improve the recognition, assessment and immediate treatment of febrile illnesses with no obvious cause in children under 5 years of age.7 The guidelines state that children aged <3 months with a temperature of 38°C or higher are in a high-risk group for serious illness and should have blood and urine tests. The guidelines also recommend performing a lumbar puncture in 1-3 month-olds who appear unwell and/or have a peripheral WBC <5x109/L or >15×109/L. Moreover, empiric parenteral antibiotics should be given to all <1 month-olds with fever, all 1-3 month-olds with fever who appear unwell and all 1–3 month-olds with WBC <5×109/L or >15×109/L.

The management of infants presenting with fever, however, remains unclear. This is particularly important in the context of the recent introduction of 4CMenB, which is associated with fever in 50-60% when administered with the other routine infant immunisations at 8 and 16 weeks of age. Parents are, therefore, advised to give prophylactic paracetamol to their infants around the time of vaccination, with two additional doses at 4-6 hour intervals. Prophylactic paracetamol has been shown to reduce the risk of fever to ~25% (similar to the rates observed when infants receive their routine immunisations without 4CMenB) without compromising the immune responses to any of the vaccine antigens in infants receiving 4CMenB vaccination with their other routine primary immunisations.15

Since 4CMenB introduction, however, several studies have reported a small increase in the number of infants presenting to primary care,6 and to hospital ED, with fever after 4CMenB vaccination, resulting in around 1,000 admissions to short-stay observation units and 1,300-1,440 admissions to the paediatric ward annually in the UK.16,17 In addition to fever, the infants often appear clinically unwell, with irritability and poor feeding, as well as vomiting and diarrhoea. Blood tests often reveal raised peripheral white blood cell counts (WBC) and C-reactive protein (CRP) levels as part of an inflammatory response to vaccination.17,18

In August 2017, the NICE guideline was amended to include a footnote stating: “*Some vaccinations have been found to induce fever in children aged under 3 months*”, without any recommendations on how to manage infants presenting to the ED with fever after vaccination. Consequently, a high proportion of infants with post-vaccination fever end up being hospitalised, have invasive investigations and receive parenteral antibiotics. In a recent retrospective audit conducted during 2016, for example, a third of infants presenting to the ED with post-vaccination fever were admitted to hospital and had blood tests for suspected IBI,19 even though serum WBC or CRP are not helpful in differentiating a vaccine reaction from an underlying IBI.

Although we have reported IBI incidence for all infants across England, our findings are consistent with published studies reporting very low rates of IBI in infants presenting with fever after the neonatal period. The risk is even lower by the time infants become eligible for their routine immunisations, especially if one only considers the narrow interval encompassing the first 48-72 hours after vaccination.

Taking our results together with the published literature, the current NICE Fever guidelines could be updated offer a more pragmatic approach to managing fever in young infants. Those aged <1 month with a temperature of 38°C or higher remain at high risk for serious illness (Red Feature), whilst those aged 1-3 months who received their routine immunisations in the previous 72 hours could be considered at intermediate risk (Amber Feature) and, therefore, warrant clinical assessment and judgement before undertaking invasive procedures or unnecessary hospitalisation for antibiotic treatment. Using this approach, infants presenting with fever after vaccination could be safely observed in hospital without invasive interventions and then discharged with appropriate safety-netting advice once their symptoms settle with regular antipyretics.

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**Ethical Approval**

PHE has legal permission, provided by Regulation 3 of The Health Service (Control of Patient Information) Regulations 2002, to process patient confidential information for national surveillance of communicable diseases.

**Competing Interest:**

None declared.

**Contributorship statement:**

SNL and AR conceived the work; KLH and SNL extracted and analysed the data. SNL, KH and AR wrote the manuscript. All authors reviewed and edited the manuscript.

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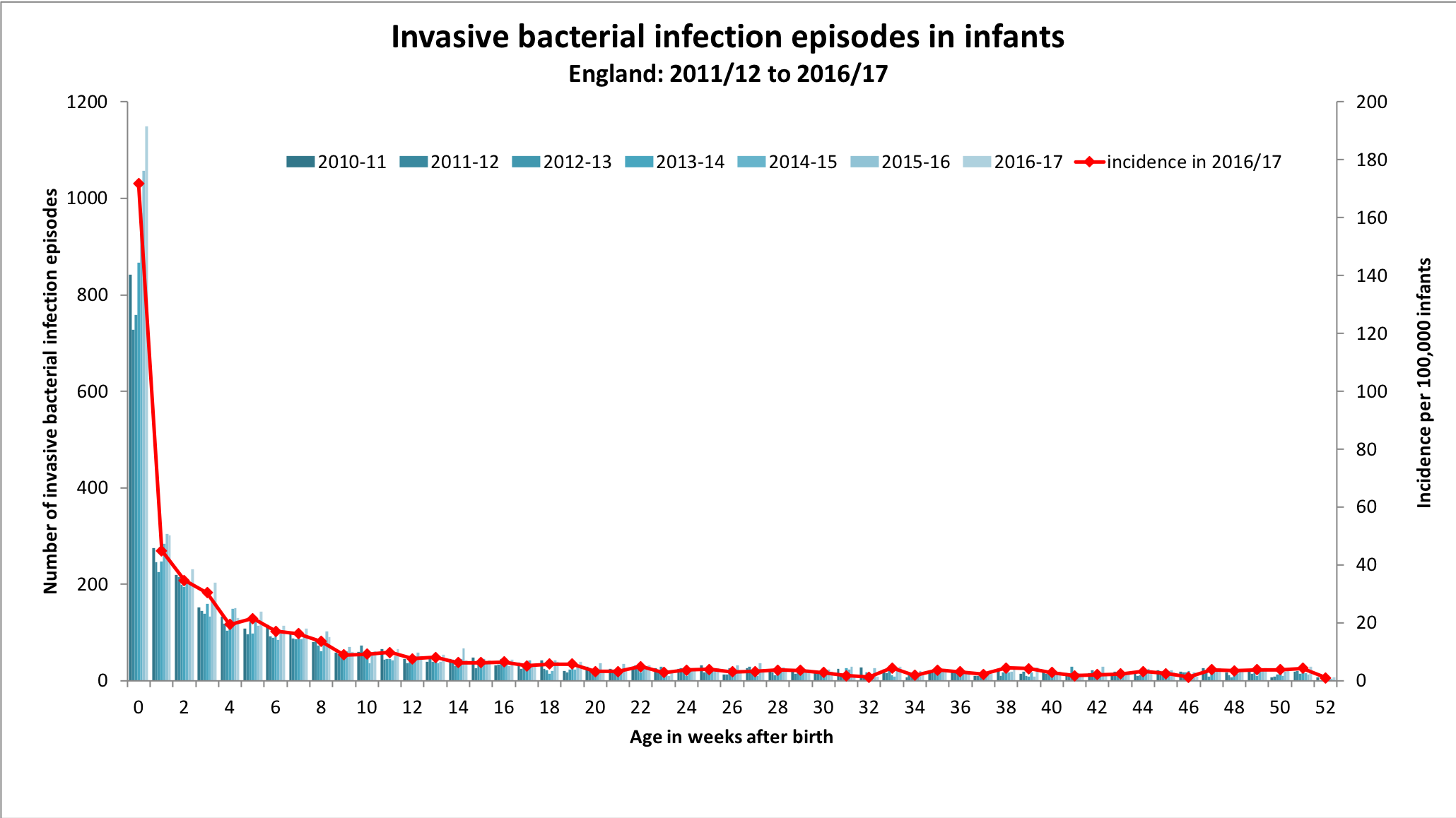
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**Table 1.** Number and incidence of neonatal invasive bacterial infections by financial year (running from April to March the following year) in England

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Financial year | Total cases in <1y olds | Incidence per 100,000 infants | Cases in <1m olds | Incidence per 1,000 live births | Cases in <3m olds | Incidence per 1,000 live births |
| 2010/11 | 3,173 | 472 | 1,490 | 2.22 | 2,210 | 3.29 |
| 2011/12 | 2,799 | 412 | 1,335 | 1.97 | 1,990 | 2.93 |
| 2012/13 | 2,810 | 403 | 1,322 | 1.90 | 1,959 | 2.81 |
| 2013/14 | 2,883 | 426 | 1,470 | 2.17 | 2,078 | 3.07 |
| 2014/15 | 3,166 | 476 | 1,592 | 2.40 | 2,270 | 3.42 |
| 2015/16 | 3,546 | 534 | 1,730 | 2.61 | 2,471 | 3.73 |
| 2016/17 | 3,698 | 552 | 1,887 | 2.82 | 2,664 | 3.98 |
| TOTAL | 22,075 | 468 | 10,826 | 2.29 | 15,642 | 3.31 |

*Figure 1.*

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*Figure 2*

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