Feidhmeannacht na Seirbhíse Sláinte
Health Service Executive

November 2006

Volume 7 Issue 11

hpsc EPI-Insight

Disease Surveillance Report of HPSC, Ireland

ISSN: 1393-9548

Contents

hpsc
Health Protection Surveillance Centre
25-27 Middle Gardiner St
Dublin 1, Ireland
Ph +353 1 876 5300
Fx +353 1 856 1299
E info@mailx.hse.ie
www.hpsc.ie

Glycopeptide-intermediate *Staphylococcus aureus* (GISA) in Ireland: First Report

The glycopeptide antibiotics vancomycin and teicoplanin play a major role in the treatment of serious staphylococcal disease. Reports of resistance and/or reduced susceptibility of meticillin-resistant *Staphylococcus aureus* (MRSA) to glycopeptides are increasing.[1] To date, six vancomycin-resistant MRSA (VRSA) isolates have been documented in the U.S.A.[2] Three types of glycopeptide resistance have been described in *S. aureus*: full vancomycin resistance {minimum inhibitory concentration (MIC) ≥16 mg/L}, glycopeptide-intermediate *S. aureus* (GISA) (vancomycin MIC 4–8 mg/L and/or teicoplanin MIC 16 mg/L) and hetero-glycopeptide-intermediate *S. aureus* (hGISA) where the majority population has a susceptible MIC but a minority population exhibit MICs in the intermediate category.[2] These definitions utilise the Clinical and Laboratory Standards Institute (CLSI) glycopeptide breakpoints that were revised in 2006[3] but previous CLSI (formerly National Committee for Clinical Laboratory Standards (NCCLS) and current British and European breakpoints define GISA as isolates with vancomycin MICs of 8 mg/L.[4,5,6]

In Ireland, glycopeptide resistance in MRSA has been monitored since 1999 in the National MRSA Reference Laboratory (NMRSARL). NMRSARL investigates MRSA isolates recovered from blood from patients in Irish hospitals that participate in the European Antimicrobial Resistance Surveillance System (EARSS), by agar screening on brain heart infusion (BHI) agar containing 6 mg/L vancomycin (BHIV6) and by the E-test macro-method with both vancomycin and teicoplanin.[7,8] Isolates showing E-test macro-method values of 8 mg/L for both vancomycin and teicoplanin or 12 mg/L for teicoplanin alone are investigated by vancomycin population analysis profile-area under the curve (PAP-AUC) ratio determination. Criteria for interpreting PAP-AUC ratios are: ≤0.89, glycopeptide susceptible *S. aureus* (GSSA); 0.9–1.29, hGISA; ≥1.3, GISA.[8]

No VRSA or GISA were detected among 2,866 MRSA isolates received in NMRSARL between January 1999 and July 2006 but nine isolates exhibited the hGISA phenotype. In August 2006, two isolates from patients in two different hospitals yielded the results shown in table 1.

Table 1. Microbiological data on two MRSA isolates with reduced glycopeptide susceptibility

Patient	BHIV6[a]	E-test[b] (mg/L)	E-test MIC[c] (mg/L)	Broth MIC[c,d] (mg/L)	PAP-AUC Ratio
1	26 colonies	12[c] (16)[e]	4.0	4.0	1.48 (GISA)
2	5 colonies	12[d] (6)[e]	4.0	4.0	1.25 (hGISA)

[a]number of colonies growing on brain heart infusion containing 6 mg/L vancomycin; [b]E-test macro-method; [c]vancomycin; [d]broth microdilution MIC; [e]teicoplanin.

According to CLSI breakpoints (from 2006) both isolates are GISA.[3] PAP-AUC analysis confirms that the isolate from Patient 1 is GISA but suggests that the isolate from Patient 2 is hGISA. Both isolates fail to meet British and European definitions of GISA. Both isolates were sent to the Bristol Centre for Antimicrobial Research and Evaluation (BCARE) and to the Centers for Disease Control (CDC, Atlanta, Georgia, USA) for confirmation. CDC reported that both isolates were GISA on the basis of MIC testing using CLSI 2006 breakpoints but BCARE could not confirm the isolate from Patient 2 as GISA because its PAP-AUC ratio fell below the criterion for GISA.

Clinical details of the two patients are summarised below. Patient 1 was a 67 year-old male who had undergone aortic valve replacement in one hospital (H1) where MRSA was recovered from blood. He was later admitted to another hospital (H2) where MRSA was again recovered and was subsequently transferred to a third hospital (H3) with endocarditis and an aortic root abscess. In H3, the patient's first blood culture isolate was susceptible to vancomycin and resistant to rifampicin. Treatment with vancomycin and gentamicin was initiated but following two weeks treatment with vancomycin, GISA was recovered from blood. Patient 2 was a 58 year-old female on renal dialysis in an unrelated hospital (H4). She had been treated with vancomycin for two two-week periods prior to detection of GISA. Intensive screening of staff and patient contacts in both hospitals yielded no secondary cases.

GISA isolates have been associated with failure of glycopeptide therapy for serious MRSA infection, may arise from GSSA during failed glycopeptide treatment, and are often associated with prosthetic materials.[1] Early reports suggested that GISA isolates were the progeny of one pandemic clone but more recent work has demonstrated the phenotype in all five major MRSA lineages. The emergence of GISA in Ireland emphasises the need for good antibiotic stewardship, the provision of sufficient resources for patient isolation, effective infection control, and adequate laboratory back-up. Failure on any of these fronts increases the risk of the emergence of MRSA with full glycopeptide resistance. To minimise the risk of this very real possibility, major efforts are needed to control the present epidemic of MRSA in Irish hospitals.

Rossney AS, Fitzgibbon MM, O'Connell B, NMRSARL

Acknowledgements
We thank the staff in EARSS participant hospitals for submitting isolates, the members of the EARSS Steering Committee and the consultant microbiologists in H3 and H4 for clinical information on these two patients. We also thank staff in the CDC and BCARE for confirmation of results.

References on request.

Outpatient Antibiotic Consumption in Ireland, 2005

Introduction

Surveillance of antimicrobial use has been identified as a key component of the Strategy for the Control of Antimicrobial Resistance in Ireland (SARI) and Ireland now fully participates in the European Surveillance of Antimicrobial Consumption (ESAC). This report covers antibiotic consumption in outpatient (sometimes referred to as ambulatory, community or primary) care areas, collected under ESAC guidelines for 2005 in Ireland.[1]

ESAC uses the WHO Anatomical Therapeutic Chemical (ATC) index to classify drugs through hierarchical levels. Consumption is measured in Defined Daily Dose (DDD), which is the assumed average maintenance dose per day for a drug used for its main indication in adults.

Methods

HPSC has purchased Irish antibiotic sales data from IMS Health, a pharmaceutical market research company. This dataset contains regional, monthly wholesaler to retail pharmacy sales data from over 95% of the wholesalers and manufacturers in Ireland. An automated data-extraction protocol was devised at HPSC to obtain the ATC/DDD outputs for antibiotics. The WHO ATC/DDD version 2005 was used throughout and retrospective data were re-analysed accordingly.

The 2002 census of population was used to calculate rates in DDD per 1000 inhabitants per day (DID) for the outpatient data.

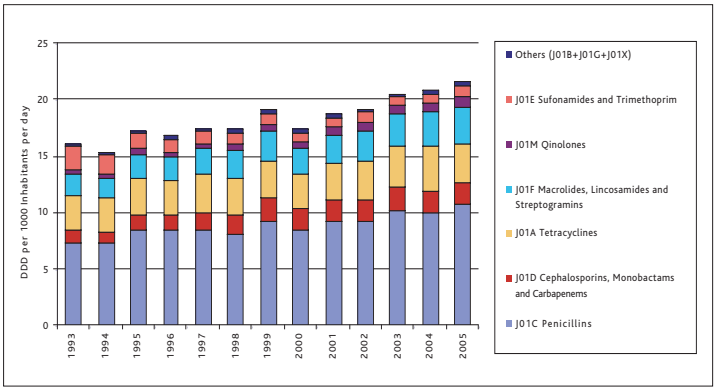

Figure 1. Outpatient antibiotic consumption in Ireland, 1999-2005

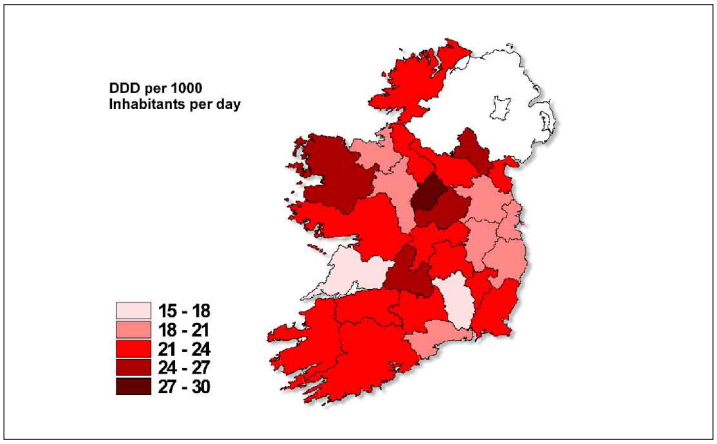

Figure 2. Outpatient antibiotic consumption by county in Ireland, 2005

For a limited analysis, a linear interpolation method was used to estimate the population for 2004 and 2005 from the preliminary census of 2006 and the final census of 2002.

Results

Overall rates

The overall outpatient antibiotic consumption for Ireland in 2005 was 21.8 DID, a rise from the previous year's rate of 20.8 DID. In 2005, outpatient consumption of penicillins accounted for the largest class used (50% of total at 10.8 DID), followed by tetracyclines (16%, 3.5 DID), macrolides (15%, 3.3 DID), cephalosporins (9%, 2.0 DID), quinolones (4%, 0.9 DID) and sulphonamides (4%, 1.0 DID). "Others" comprising aminoglycosides and miscellaneous accounted for 2% at 0.4 DID.

The outpatient rates using the interpolated population estimates were 20.1 DID for 2004 and 20.5 for 2005, a rise of 2%.

Figure 1 shows consumption of antibiotics in outpatient care, in DID, for Ireland since 1993. Antibiotic usage has been rising steadily from 16.2 DID in 1993 to 21.8 DID in 2005, and was 23.8 DID for the last quarter of 2005.

Regional variation

There was some variation in outpatient antibiotic usage among the different HSE areas (20.6 to 25.3 DID). However, as shown in figure 2, there was considerable variability in outpatient antibiotic usage at county level (17.3 to 28.7 DID).

Seasonality

Overall antibiotic use was highest during winter. For the complete dataset of 13 years (1993-2005), the mean difference between troughs (quarters 2 and 3) and peaks (quarters 1 and 4) in antibiotic use was 23% (range 12% - 34%), and 15% for 2005.

The fluctuation in outpatient antibiotic utilisation during the course of a year is further demonstrated in figure 3. The mean monthly rate for the last five years (2000-2004) dropped steadily from January to July and stayed low for August. The level rose sharply to a plateau in September, October and November then peaked in December. The pattern was the same for 2005, but was higher than the mean rate for the previous five years, particularly in the months March through to June.

Penicillins

Figure 4 shows the breakdown of penicillin usage by subclass in outpatients. Penicillin in combination with a beta-lactamase inhibitor (such as amoxicillin/clavulanate) accounted for the largest proportion of penicillins and showed a dramatic rise over the last six years (2000-2005). Broad-spectrum penicillins (such as ampicillin and amoxicillin) usage was stable but high. Beta-lactamase resistant penicillins (such as flucloxacillin) and

narrow-spectrum penicillins (such as benzylpenicillins) usage were lower but showed slight increases.

Cost estimates

According to IMS data, which represent private and non-private community antibiotic sales, the total ingredient cost of antibiotics for 2005 was €51.7 million. This is a rise of 5% from 2004 when the cost was €49.5 million. The HSE National Shared Services Primary Care Reimbursement Service (formerly GMS Payments Board) stated that the antibiotic ingredient cost for 2004 under its three main schemes was €29.7 million, which is 60% of the total cost (private plus GMS) while the eligible persons only represent about 30% of the population.[2]

Discussion

Although the IMS dataset used in this report is very comprehensive the data do have some limitations. Firstly, the data are based on pharmacy wholesale data rather than on individual prescriptions. Thus the data cannot be used to determine the actual number of antibiotic courses taken and do not provide information on dose or duration of therapy. Factors such as stockpiling of antibiotics in pharmacies and drug wastage (e.g. when antibiotics pass their sell-by date) may introduce biases that cannot be corrected for within the current database. Nevertheless the data do show consistency over time and similar data sources have been successfully used to calculate antibiotic consumption in other countries. Furthermore, the HPSC is due to begin a project to collect antibiotic usage data directly from a sample of retail pharmacies in Ireland.

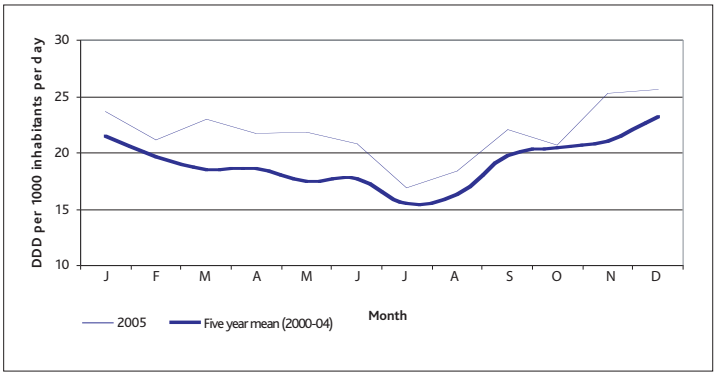

Figure 3. Variation in outpatient antibiotic consumption by month in Ireland, mean of five years (2000-2004) and 2005

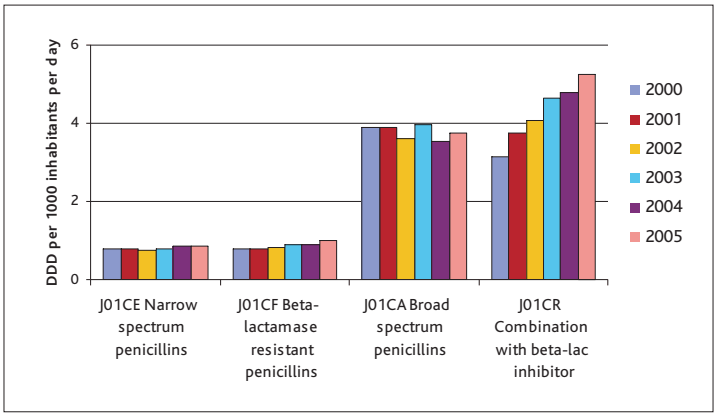

Figure 4. Outpatient consumption of penicillin subclass in Ireland, 2000-2005

In an ESAC report of 2002 data for 32 EU countries, the range of outpatient antibiotic usage was 10.0 DID (the Netherlands) to 32.2 DID (France).[3] Outpatient antibiotic usage in Ireland was 21.8 DID for 2005 and has been around 18-21 DID over the last 5 years. Therefore, the rate in Ireland is mid-range in Europe. However, the marked seasonal fluctuation coupled with a higher proportion of broad-spectrum penicillin consumption in Ireland is consistent with those countries having a higher level of resistance among key indicator pathogens, as in Portugal and Italy, unlike the Nordic countries, which generally have low levels of resistance. Furthermore, the overall outpatient antibiotic usage, particularly penicillins such as amoxicillin/clavulanate, is increasing.

Outpatient antibiotic usage in some Irish counties appears to be considerably different from the national rate (range 17.3 DID to 28.7 DID, in 2005). This regional variation is similar to the pattern from 2004 and may reflect differences in prescribing practices, socioeconomic factors, or pharmaceutical marketing.[4] This is further supported in the analysis of the GMS data, which showed that those entitled to reimbursement (representing 30% of the population) are prescribed about 60% of the antibiotics in terms of cost. Seasonal fluctuation (range 16.9 DID to 25.6 DID, in 2005) has been seen every year in outpatient antibiotic consumption and is probably related to over-prescribing of antibiotics for respiratory tract infections in winter months.

The three factors – regional, seasonal, and socioeconomic – may work together to produce very high rates of antibiotic consumption in some primary care areas at certain times, resulting in increased pressure for selection of resistant variants of important bacterial pathogens. Promoting the prudent use of antibiotics requires education of prescribers and the general public. The data presented in this report suggest that this should focus on reduction of prescribing for respiratory tract infections, particularly during the winter months, and promoting the use of narrow spectrum antibiotics over broader spectrum agents. The SARI Community Antibiotic Stewardship Sub-Committee is currently involved with regional community-based multidisciplinary teams to target reduction of antibiotic consumption in Ireland in the coming years.

Ajay Oza, Robert Cunney, HPSC

Acknowledgements

HPSC wish to thank the Information Management Unit at DoHC for the hospital activity data, IMS Health and the ESAC management team.

References

1. ESAC II (2004-2007). DG/SANCO Agreement Number No. 2003211. Available at www.esac.ua.ac.be/.
2. General Medical Services (Payments) Board. Financial and statistical analysis of claims and payments – 2004. Health Services Executive.
3. Goossens H *et al*. Outpatient antibiotic use in Europe and association with resistance. *Lancet* 2005; **365**: 579-87.
4. HPSC Annual Report 2004. Available at www.hpsc.ie.

Invasive *Haemophilus influenzae* Disease in Ireland, 2005/2006

Background

The incidence of invasive *Haemophilus influenzae type* b (Hib) disease declined in Ireland following the introduction of the Hib conjugate vaccine in 1992.[1] However, from late 2004 a resurgence in Hib disease was seen, with most cases occurring in vaccinated children.[2] This increase led to concerns that a three-dose infant schedule was no longer sufficient to maintain long term protection. A similar situation had already emerged in the UK.[3] In response to this emerging trend in Ireland, a catch-up campaign offering a Hib booster dose to children <4 years of age was launched in November 2005.

This paper reviews the epidemiology of invasive *H. influenzae* disease from July 2005 to June 2006 (2005/2006) using enhanced notification data. Data were extracted from the Computerised Infectious Disease Reporting (CIDR) system on the 4 October 2006.

Results

Invasive *H. influenzae* disease

In 2005/2006, 42 cases (1.1/100,000 population) of invasive *H. influenzae* were notified. These notifications ranged in age from 2 months to 83 years. The disease was more common in males (M:F 1.8:1.0). The number of *H. influenzae* notifications in 2005/2006 was almost identical to the same period last year when 43 cases were notified (figure 1). However, the difference between the two years was the decline in Hib cases and the increase in invasive infection due to non-capsular isolates. Hib accounted for just 33% (n=14) of the *H. influenzae* notifications in 2005/2006 compared to over half in 2004/2005 (53%; n=23). In contrast, the number of cases due to *H. influenzae* non-capsular strains increased from nine in 2004/2005 to 19 in 2005/2006. The majority of these non-capsular cases occurred in elderly adults aged 69 years and greater (n=11). Two arose in middle-aged adults and the remainder (n=6) in children <10 years of age (age range 16 months – 9 years). The remainder of invasive *H. influenzae* infections in 2005/2006 were due to type e (n=2), type f (n=1), isolates not typed (n=3), and typing results pending (n=3).

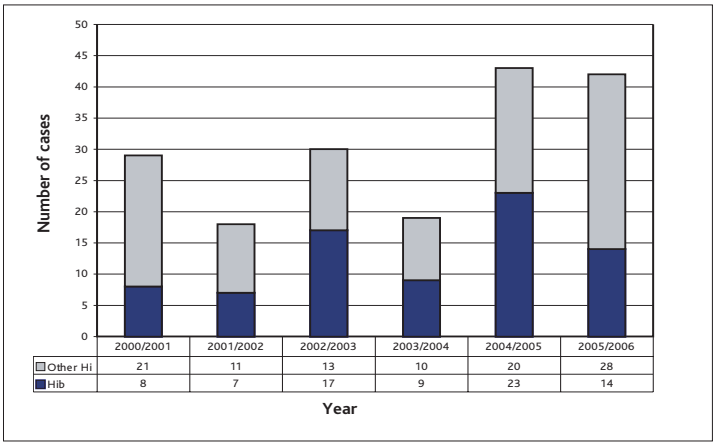

Figure 1. Number of invasive Haemophilus influenzae notifications in Ireland, by the epidemiological year, July to June

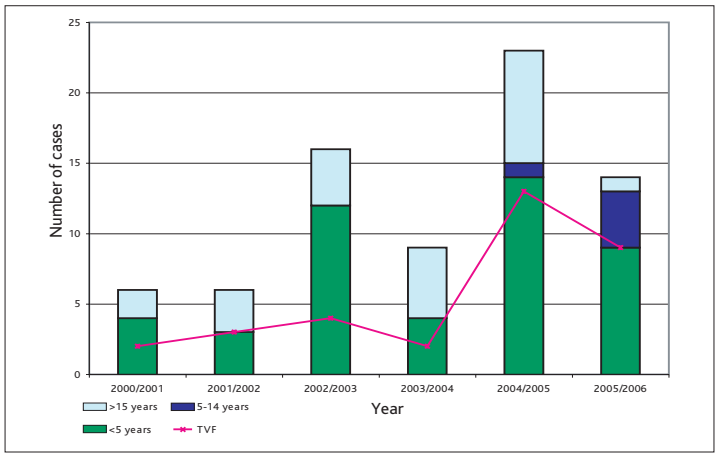

Figure 2. Number of invasive Haemophilus influenzae type b notifications in Ireland by epidemiological year (July - June) and age group and the total number of true vaccine failures reported each year

Invasive *H.influenzae* type b disease

The number of Hib cases declined from 23 in 2004/2005 to 14 in 2005/2006 (figure 1). These 14 Hib cases occurred predominantly in children; four in <1 year olds, five in 1-4 year olds, three in 5-9 year olds and one in 10-14 years. Just one Hib case occurred in an adult (7%; 1/14). A greater proportion of Hib cases occurred in adults in 2004/205 (35%; 8/23). The clinical manifestations of Hib disease in the 13 children were: epiglottitis (n=4), septicaemia (n=4), meningitis (n=3), meningitis and septicaemia (n=1), and cellulitis (n=1). A decline in Hib cases in 2005/2006 was seen in <5 year olds and in adults when compared with the previous year (figure 2). In contrast, there was an increase in the number of notifications in 5-14 year olds from one to four cases (figure 2).

Hib vaccine failures

In 2004/2005, a peak in true Hib vaccine failures (TVFs) was experienced in Ireland when 13 TVFs occurred. The number of TVFs dropped to nine in 2005/2006 (figure 2). Although not as low as the levels seen in the years prior to 2004/2005 (range 1-4 TVFs per year), no TVF occurred in the last quarter of 2005/2006 (Q2-2006). This is the first quarter since Q1-2004 that there have been no TVFs. The nine TVFs reported in 2005/2006 ranged in age from 14 months to 14 years (1-4 years n=5; 5-9 years n=3; 10-14 years n=1). In 2004/2005, 12 of the 13 TVFs were in 1-4 year olds and one other case was in a 5-9 year old. Overall, in 2005/2006, six of the TVFs occurred between July and December 2005 and the remaining three between January and March 2006. The last three TVFs to occur have been in 5-9 year old children which overall is a slightly older age profile than those that have occurred in the past.

Discussion

In 2004/2005, an increase in Hib cases in children under 5 years occurred in Ireland. An increase of similar magnitude occurred previously (2002/2003). However, this time there was a difference. The Hib cases in 2004/2005 were occurring predominantly in fully vaccinated children whereas in 2002/2003 cases were mainly in unvaccinated children. In 2004/2005, there were 13 TVFs, whereas in the years prior to this, the number never exceeded four per year. To provide further protection against Hib disease, a catch-up campaign commenced in Ireland on 21 November 2005, offering a Hib booster dose to children <4 years of age.

In 2005/2006, although the overall number of invasive *H. influenzae* cases did not change compared to the previous year, the number of Hib cases declined and the number of non-capsular cases increased. The decline in Hib cases in 2005/2006 was largely due to a decrease in the occurrence of adult cases. No major change in the number of Hib cases in the <15 year olds was seen between the two years (13 in 2005/2006 and 15 in 2004/2005). The main difference within this age group was that there was a decline in the number of Hib cases in the <5 year olds and an increase in the 5-14 year olds in 2005/2006. Another change in 2005/2006 was the number of TVFs decreased from 13 to nine. This decline was even more dramatic when TVFs in <5 year olds were examined, with five occurring in 2005/2006 as opposed to 12 in 2004/2005. The reduction of Hib cases and TVFs in the <5 year olds would indicate that the Hib booster catch up campaign is having an impact in protecting this age group from Hib disease. To ensure the ongoing protection of young children from invasive Hib disease in Ireland, the inclusion of a routine Hib booster to the childhood immunisation schedule at 12 months of age has been approved by the HSE and is effective from 18 September 2006.

Margaret Fitzgerald, Suzanne Cotter, Darina O'Flanagan, HPSC

Acknowledgements

HPSC wish to thank all who have contributed to the surveillance of invasive *H. influenzae* disease in Ireland – staff in the departments of public health, microbiology laboratories and hospital clinicians.

References available on request