EPI-INSIGHT

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DISEASE SURVEILLANCE REPORT OF NDSC, IRELAND

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IN THE NEWS!

VCJD and BSE in Ireland

Variant Creutzfeldt Jakob Disease (vCJD) is a progressive fatal neurological disease in humans (Incubation Period: 5 to 30 years). The average age at onset of illness is 28 years with a mean duration of illness from onset of symptoms to death of 13.5 months.

Link between vCJD and BSE: A geographical association exists as the majority of bovine spongiform encephalopathy (BSE) cases occurred in the UK and 95 of the 98 cases, world-wide, of vCJD were reported there. The emergence of BSE preceded vCJD indicating a temporal association. Studies of stored human brain tissue internationally have not identified the histopathological changes characteristic of vCJD prior to the current BSE epidemic. Incubation period and pathological lesion studies in mice and molecular typing studies demonstrate that vCJD is similar to BSE but different from other transmissible spongiform encephalopathies.

Risk Factors: Humans may have been exposed to the BSE agent through different routes including consumption of contaminated food, contaminated alternative medicines, contaminated pharmaceutical products, medical instruments, transplants, blood donations and cosmetics. The consumption of beef is not a risk factor for vCJD, rather it is the consumption of contaminated beef products. Current information indicates that BSE infectivity resides in brain, spinal cord and other specified risk material (SRM). The consumption of this material is high risk and possibly exposure to BSE may only have occurred in those who may have eaten such material.

vCJD in Ireland: Currently, in Ireland, there is a BSE epidemic in cattle but smaller than the British epidemic. However, Ireland does not have a vCJD epidemic in humans. One case of vCJD has occurred in an Irish woman who resided for a long period in the UK. The likelihood of a human epidemic occurring is unknown. Food borne exposure in Irish people may have been minimal as the consumption of beef products containing mechanically recovered meat, which would have contained SRM was not widespread here.

It is possible that foodborne exposure occurred in Irish people as follows:

1. Those who consumed contaminated beef products while residing in the UK during the BSE epidemic peak (mid-80s and mid-90s), approximately 236,000 people have returned from the UK to live in Ireland since 1987.
2. Those who may have eaten contaminated beef products on visits to the UK. (on average there are over 2 million visits per year by Irish people to the UK)
3. Those who may have eaten contaminated British beef products imported into Ireland, before 1996 when importation of British beef was banned (approximately 3000 tons of beef products had been imported annually).
4. Those who may have eaten contaminated beef products from, or in, other EU member states
5. Those who may have been exposed to contaminated beef products from Irish animals

Cases of BSE in Ireland are confined to animals born in 1996 or earlier. From 1997, Ireland has had an effective ruminant meat and bone meal (MBM) ban, and high temperature and pressure rendering making it unlikely that animals born after this date had access to contaminated MBM and could therefore be incubating BSE. SRM is removed from all animals over 12 months of age, irrespective of year of birth and animals over 30 months are subjected to the post mortem "Enfer test".

Dr Patrick Wall, FSAI.

Developments in National Disease Surveillance

Astron, the IT consultants hired to define the information needs of NDSC and its partners for electronic surveillance of infectious diseases, have completed their work. CIDR Board accepted their recommendations in December 2000. In Aston's view no existing systems have been identified which meet the criteria defined as necessary and so they recommend building a new system. This system would comprise a national core database to store information for management and notification of cases of infectious disease, with on-line access for CIDR partners. Astron also recommend a structure for developing the system and for supervising the operation of the system. A project team for CIDR is being assembled at NDSC, and this team will have external project management assistance. In addition each health board has been asked to nominate a person to the CIDR Supervisory Committee, which will have a national operational role. Each health board will develop business rules for participation in the system. A committee chaired by the CEO supervisory committee representative will be set up in each health board to do this. Regular updates on the progress of this important project will be posted in Epi-Insight. The collection of data on local laboratory practices in relation to notifiable

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A TEENAGE TUBERCULOSIS CLUSTER

Introduction

The largest school cluster of tuberculosis (TB) cases nationally over the past decade is described. Several noteworthy features integral to the investigation and management of this sizeable outbreak are highlighted.

Investigation

The first student case (15 year old male) was diagnosed in mid-August 1999, following presentation to the family doctor and referral for specialist opinion. A cavity was present on chest x-ray. Sputum was positive on direct microscopy. The teenager had been symptomatic for months. Three household contacts were found, on contact tracing, to be cases. The original source of infection was never definitively identified.

The second level school which the student attended was a co-educational day school (students aged 12-19 years), with a population of 316 students and staff. Screening of school contacts, comprising tuberculin skin tests (Mantoux 2TU) and chest x-rays as indicated, followed national guidelines.[1] Initially the student's classmates, other close contacts and all staff were offered screening.

An Outbreak Control Team (OCT) was convened. A phased approach to further school screening was adopted. Those at most risk (*i.e.* closest contacts) were screened first. Review of screening test results following each phase indicated whether extension of screening to those with less contact was necessary. There was initial extension to Second Years through to the Leaving Cert Year. This was followed by screening of First Years, Leaving Cert students of the previous year who had left school before the summer holidays and recently retired staff. First Years had not been included in the earlier screening round as they were considered not to have been exposed to the index case.

An emergency meeting of the Health Board's Regional Collaborative TB Committee was held to advise on the strategy for screening extension beyond the school. Based on the collated screening results, it was agreed that older teenagers were the group that needed targeting. A consensus decision was made to include the two other secondary schools in the town, associated school buses and sports clubs, so as to best target the age groups concerned. Primary schools were not included. In all, over 1,200 students, ex-students and school staff were screened. All students who had a negative tuberculin response on the second round of screening were offered BCG vaccination, provided they had not received the vaccine previously and there were no contraindications.

Results

All thirteen teenage cases detected were connected with the original school (Table 1). Seven were female; six male. Ages ranged from 14-19 years. Twelve had pulmonary disease, four of whom had signs of cavitation on chest x-ray. Three cases were infectious i.e. *sputum positive on direct microscopy*.[2] Five were culture positive (all M.*tuberculosis*). Those with extrapulmonary disease had pleural effusions. The last case notified was resistant to Isoniazid. The majority of cases were asymptomatic. None of the thirteen cases had previous BCG vaccination.

Table 1. Student Case Details

Case	Age	Sex	TB Site	Infectious	Culture
1*	15yrs	M	Pulm (cavity)	Yes	Pos
2	14yrs	M	Pulm (cavity)	No	Neg
3	14yrs	F	Pulm	No sputum	Not done
4	14yrs	M	Pulm	No	Neg
5	14yrs	F	Pulm	No sputum	Not done
6	14yrs	F	Pl.Effusion	No sputum	Not done
7	14yrs	F	Pulm	No sputum	Not done
8	14yrs	F	Pulm	No	Pos
9	15yrs	M	Pulm & Pl.Effusion	No	Pos
10	17yrs	M	Pulm	No sputum	Not done
11	19yrs	M	Pulm (cavity)	Yes	Pos
12	18yrs	F	Pulm	No	Neg
13**	16yrs	F	Pulm (cavity)	Yes	Pos
*First Case-August 1999 **Last Case-January 2000					

There was a concentration of cases in the Third Year group (8); the remainder of the cases occurred in Fourth Year (2); Current Leaving Cert. Year (1); Previous Leaving Cert.Year (2). No cases were found among the First or Second Year students. Case attack rates by school year are depicted (Figure 1).

Antituberculous prophylactic therapy (Isoniazid for six months) was indicated for over sixty student contacts, predominantly mid-to-late teen age, on the basis of screening test results.

Prophylaxis rates among students reflected, as did case attack rates, the higher concentration of tuberculous infection among older teenagers in the school (Figure 1).

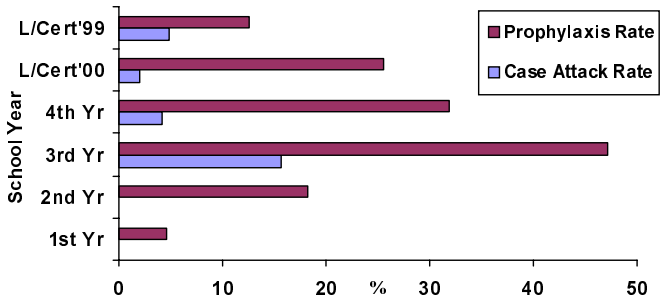

Figure 1: Case Attack Rates & Prophylaxis Rates by School Year

Screening of the other secondary schools at the time (combined population 817) detected no further cases; seven students were commenced on prophylactic antituberculous therapy.

Discussion

Features of interest associated with the investigation and management of this outbreak included: the protective effect of BCG vaccination, the booster phenomenon, the issue of compliance, communication and public concerns.

BCG: a protective effect?

The cluster presented a unique opportunity to examine whether or

not prior BCG vaccination conferred a protective effect among the students of the school where the index case occurred. Two-thirds of this student population had not received prior BCG vaccination; a BCG policy focusing on 'at-risk' groups operated in the community care area in which the school was located. The remaining one-third of students in the school had been vaccinated as they came from adjoining areas of the Mid-Western and South-Eastern Health Boards, both of which Boards operated neonatal or school-leaving (11 years) BCG policies. Those regarded as having had BCG vaccination had BCG scars present, or a record of vaccination, or both.

None of the cases had prior BCG vaccination (Table 2). The difference in incidence of TB between teenagers who had been vaccinated and the non-vaccinated teenagers was statistically significant (Fisher's Exact Test/ 2-sided: 0.005). The estimated relative risk of non-vaccinated teenagers getting TB as compared to vaccinated teenagers was 7.3.

Table 2. TB Cases vs BCG Vaccination

		TB Case		
		Yes	No	Total
BCG Vaccination	Yes	0	75	75
	No	13	133	146
		13	208	221
n=221 students (excludes 1st Years & include Post L/Certs				

BCG has long been, and continues to be, a controversial vaccine.[1] Expert opinion varies on its effectiveness. However, analysis of this teenage case cluster supported the protective efficacy of previous BCG among this teenage population in the Irish context. A school outbreak in Donegal, almost fifteen years ago, also suggested a significant protective effect of BCG vaccination against TB among the adolescent school population screened.[3]

Compliance

Compliance is a major determinant of the success of drug treatment – compliance of the physician in prescribing the optimum appropriate regimen and monitoring it, and compliance of the patient in taking the medication as prescribed.[4] Throughout the course of the outbreak, particular emphasis was directed to the need for constant vigilance for evidence of non-compliance both among cases and those on prophylactic treatment. Close liaison existed between public health doctors and treating physicians. Directly observed therapy was necessitated in one case to ensure compliance. The supervision was home based, carried out by local public health nurses. The importance of compliance is central to preventing the emergence of drug resistance.[1] One of the school cases was Isoniazid resistant. Isoniazid prophylaxis had been indicated for this student some months earlier, following screening. However, compliance problems were not found to be a factor.

Booster Effect?

No consensus exists regarding the definition and interpretation of a significant boosting reaction after sequential tuberculin testing.[5] In young adults, booster reactions due to previous tuberculous infection have been found to be uncommon.[5]

In the course of the investigation, an interesting phenomenon was noted among a subgroup of the First Year class. First Years, on balance, were considered unlikely to have been exposed to infection. The subgroup in question had received BCG vaccination six months previously in another Health Board area. These students were found to be tuberculin negative on the first round of screening. On retesting in the second round they were tuberculin positive. The question arose as to whether these were true converters or if the booster effect was being observed. Expert advice was obtained. It was generally agreed that the booster phenomenon was the explanation. Nevertheless, all were followed up closely.

Communication

Not surprisingly, the TB cluster presented a significant challenge on the communications front. There was public anxiety, family doctors were inundated with queries and the media was intensely interested The school felt stigmatised within the locality, students felt ostracised within the school and parents were extremely concerned. A multi-targeted, timely, frank and open communications exercise was executed at a number of levels:

- School staff met individually/group by public health doctors.
- Parents offered appointments to attend school while children being screened; open access for parents to public health doctors facilitated
- Students met individually by public health doctors/nurses.
- Information leaflets distributed to staff, parents and pupils.
- Public parent meeting held in the school. Parents, staff, students and public representatives attended.
- Public information phoneline operated.
- Family doctors updated regularly and meeting convened.
- Regular media updates given. Health Board's Communications Department actively involved at all stages. Representative was invited to each OCT meeting and also attended public parent meeting.

Public Concerns

Particular concerns which were raised and addressed included - the question of school safety; why the school was not closed; the risk of contracting TB; the rationale for the phased screening process; why the primary schools were not screened; the side effects of antituberculous treatment, BCG vaccination policy, the effectiveness of BCG vaccine and whether or not there was any link between cases and bovine TB.

Conclusion

This was a significant micro-epidemic of TB associated with a second level school. The dedicated input of front-line public health professionals over a prolonged period was critical to successful management of the cluster. The level of risk communication demanded was challenging. Of particular note was the subsequent demonstration of the protective effect of previous BCG vaccination among the teenage population concerned.

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Dr Margaret O Sullivan & Dr Maeve Burke, Southern Health Board

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HIV Resistance testing: A new dimension in HIV patient care management

It is now widely accepted that the development of resistance to antiretroviral drugs is a major cause of failure of combination therapy in HIV-1-infected individuals. As more information regarding the basis of this resistance emerges, HIV drug resistance testing is quickly moving from the research laboratory to the diagnostic laboratory. Indeed, recent structured clinical trials have demonstrated the value of resistance testing as a prognostic indicator of response to therapy[1,2]. With the recent rise in the number of newly diagnosed HIV positive individuals in Ireland (annual figures for 1998, 1999 and 2000 were 136, 209 and 320 respectively) optimisation of patient care management should remain of paramount importance.

Diagnostic techniques (HIV genotypic resistance assays) have recently become available which allow detection of such drug resistance by monitoring changes in the two main HIV proteins targeted by antiretroviral therapy (reverse transcriptase and protease). The reports that are generated contain a list of all FDA-approved antiretroviral drugs for treatment of HIV and flag any changes which are relevant for resistance (Table 1). The rational selection of combinations of drugs to avoid or overcome resistance is now accepted as one of the critical challenges to achieving long-term viral suppression and optimal clinical outcome.

Implementation of resistance monitoring at the National Virus Reference Laboratory (NVRL) has uncovered extensive resistance patterns in the Irish antiretroviral experienced population (those receiving combination therapy). Resistance profiles from a cohort of 40 treatment experienced patients have shown all patients to have some form of resistance to the reverse transcriptase inhibitor class of drug while 68% contain resistance related mutations to the protease inhibitor class. Preliminary studies into the clinical value of such tests in Irish patient care management have shown the importance of this new facet in the fight against HIV disease. Drug regimens of 23 HIV patients failing therapy were reassessed based on genotypic resistance, previous exposure and viral load . The impact of the newly prescribed regimen was measured after 3 months and all 23 patients displayed a clinically significant drop in viral load (unpublished data).

Fundamental questions such as the prevalence of resistance in antiretroviral naïve patients in Ireland can now be addressed. We have shown the prevalence of primary drug resistance in an antiretroviral naïve cohort of 50 newly diagnosed patients to be 6% (unpublished data). Although this figure is low compared with similar data emerging from the rest of Europe (5-15%) it may support the routine use of resistance testing at initiation of therapy.

When considering the use of routine diagnostic resistance testing, one must bear in mind that the cost of a single test which is approximately the same as two weeks of combination antiretroviral therapy. However, as more data emerges the benefit both clinically and pharmacoeconomically of assigning regimens on an individual patient basis is becoming evident.

Dr S.Coughlan PhD, NVRL.

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Relevant Reverse Transcriptase (RT) Mutations: M184V

Nucleoside RT Inhibitors	Resistance Interpretation
zidovudine	No evidence of resistance
didanosine	*Partial Resistance*
zalcitabine	*Partial Resistance*
lamivudine	**Resistance**
stavudine	No evidence of resistance
abacavir	*Partial Resistance*
tenofovir	Insufficient Data
foscarnet	Insufficient Data

Non-nucleoside RT Inhibitors	
nevirapine	No evidence of resistance
delavirdine	No evidence of resistance
efavirenz	No evidence of resistance

Relevant Protease Mutations: D30N M36IL90M

Protease Inhibitors	Resistance Interpretation
saquinavir	**Resistance**
indinavir	*Partial Resistance*
ritonavir	*Partial Resistance*
nelfinavir	**Resistance**
amprenavir	*Partial Resistance*

Resistance Interpretation is based upon an international expert panel interpretation of *in vitro* phenotypic and *in vitro* virologic response data available as of February 2000 for correlation of Protease and RT sequences to antiretroviral drug resistance. These include primary and secondary mutations.

Figure 1: The HIV resistance assay (Visible Genetics Inc.) depends on amplification of the HIV-1 protease and reverse transcriptase genes from viral RNA in plasma. This region of the HIV genome is then sequenced to give a genetic fingerprint of the virus. The sequence information is then analysed using software which compares it to a database of known resistance mutations. The mutations are identified by an amino acid change on the protein, e.g. M184V indicates achange from methionine to valine at position 184.

Continued from page 1

diseases is nearing completion. Only a few responses remain uncollected. The report of the Subgroup of the Scientific Advisory Committee on the Strategy for Control of Antimicrobial Resistance in Ireland (SARI) will be published shortly. Funds have been made available from the Department of Health & Children at health board level for improving communications between NDSC and all partners in surveillance of disease at regional level and for implementation of SARI/CIDR and other surveillance activities. Several participant laboratories in the European Antimicrobial Resistance Surveillance System (EARSS) have requested and received a free software application for analysis of antimicrobial resistance (AMR) data called WHONET 5. It is hoped that this will prove useful in collecting AMR data for EARSS and serve a tool for AMR analysis locally.

Salmonella Monthly Report (January 2001):

Strains are allocated to months based on the date of receipt of the isolate from the referring laboratory. These figures are provisional as work may not be finished on particular strains at the time of publication. Data are provided courtesy of Prof Martin Cormican and Dr Geraldine Corbett-Feeney, INSRL.

Health Board	E	M	MW	NE	NW	SE	S	W	Total
S.Typhimurium	5	3	1	0	0	0	2	0	11
S.Enteritidis	1	0	0	1	1	3	4	1	11
S.Bredeney	2	0	0	0	0	0	0	0	2
S.Cerro	0	1	0	0	0	0	0	0	1
S.Dublin	0	1	0	0	0	1	0	0	2
S.Haifa	1	0	0	0	0	0	0	0	1
S.Infantis	0	0	0	0	0	1	0	0	1
S.Johannesburg	0	0	0	0	0	2	0	0	2
S.Kentucky	1	0	0	0	0	0	0	0	1
S.Newport	0	0	0	1	0	0	0	0	1
S.Schwarzengrund	0	0	0	0	0	0	0	1	1
S.Stanley	1	0	0	0	0	0	0	0	1
S.Uganda	1	0	0	0	0	0	0	0	1
S.Veneziana	0	0	0	0	0	0	1	0	1
S.Virchow	0	0	1	0	0	0	0	0	1
Total	12	5	2	2	1	7	7	2	38