



**TRUSTEES REPORT
EXTRACTS - YEAR TO 30 SEPTEMBER 2001**

Significant events

*The significant events in the year ended 30 September 2001 were as follows:

(i) Epidemiological surveillance of Reye's Syndrome

The objectives of this project are to describe the epidemiological and clinical features of Reye's Syndrome (RS) in children in the British Isles, to monitor long term trends, and to provide a database for detailed clinical, laboratory, and aetiological studies. The work is undertaken by Dr Susan Hall, consultant epidemiologist and honorary lecturer in the Department of Paediatrics, Sheffield University; and by Mr Richard Lynn, research officer at the Royal College of Paediatrics and Child Health (RCPCH).

Surveillance of RS began in August 1981 as a venture shared between the (then) British Paediatric Association and the Public Health Laboratory Service Communicable Disease Surveillance Unit (CDSC). Responsibility for case ascertainment was transferred to the British Paediatric Surveillance Unit (BPSU) of the RCPCH in June 1986 and from CDSC to the Department of Paediatrics at Sheffield in 1995. From this point onwards the surveillance scheme has been supported entirely by the National Reye's Syndrome Foundation of the UK. The grant holder is Professor David Hall, Sheffield Centre for Health and Related Research, Sheffield University.

In addition to BPSU reporting, cases are also ascertained via death entries provided by the Office for National Statistics, the General Registry Office for Scotland, the Northern Ireland Statistics and Research Agency, and via laboratory reports to CDSC.

There is increasing recognition that a number of inherited metabolic disorders - most notably those affecting fat oxidation and ureagenesis, may present as a 'Reye-like' illness, clinically and pathologically indistinguishable from classic RS. The surveillance questionnaire therefore seeks information on whether patients have been investigated for these disorders.

The surveillance scheme ended in April 2001 because so few cases of classic RS were occurring and because of competition for space on the BPSU report card from other projects.

Annual Report

The report for the period 1 August 1999 - 30 April 2001 was published in the BPSU Annual Report in September 2001. Key findings were as follows:

Between August 1981 and April 2001 a total of 632 suspected cases of RS were reported but the diagnosis was subsequently revised in 164 (26%). Eighty one (49%) of the revisions were to one of the 'Reye-like' inherited metabolic disorders. Two hundred and thirty nine (53%) of the total 450 cases compatible with a diagnosis of RS died.

In the year to 31 July 2000, four reports of new cases were received and further information was provided on all of them. One of the four diagnoses was later revised,



Annual Report (continued)

leaving three patients whose clinical and pathological features were compatible with the case definition of RS. Three of the cases were first reported via the BPSU, one was ascertained only via a death entry.

In the period 1 August 2000 to 30 April 2001, three reports were received, further information was provided on two. One of the diagnoses was later revised; in the other case a specific alternative diagnosis was not reached, but an inherited metabolic disorder was so strongly suspected that RS was not recorded as a cause of death.

This Annual Report was the last in the series which started in 1981/82, when surveillance of RS began. As the first clinical reporting scheme involving paediatricians in the UK and Ireland in the epidemiological surveillance of rare disorders of public health importance, the RS surveillance scheme was a forerunner of the BPSU. It is fitting that the total cases in the last complete surveillance year, three (none of whom had classic, aspirin associated RS) equalled the lowest total recorded in 19 years and that, up to the end of surveillance in April 2001, there were no cases at all. It is fitting because the trends vindicate the public health action taken on the use of aspirin in children in 1986 which, as also reported in the United States, represents a triumph for primary prevention of a devastating childhood illness.

National surveillance of RS through paediatrician reporting has now ceased, but two important issues remain:

First - *classic, aspirin-associated Reye's syndrome* has now become so rare that some clinicians have dismissed it as being no longer of any clinical importance. However, this is a dangerously complacent view of a disease capable of re-emergence during a major influenza epidemic or pandemic (it is now 10 years since the annual influenza incidence rose to epidemic levels and even these were not as high as in the last major epidemic in the 1970's) if aspirin warnings are disregarded or ignored because the child is over 12. The decline of RS means that a new generation of paediatricians in training and young consultants will certainly never have seen or heard about a case and are unlikely to have read about it or had it included in educational materials. Furthermore, it is likely to be under-recognised by physicians caring for teenagers and older adults with acute encephalopathy. Thus if there is a resurgence, the "old days" of late diagnosis, late or inappropriate treatment and poor outcome in terms of mortality and brain damaged survivors may be seen again.

It is, therefore, most important that RS is not forgotten or removed from the differential diagnosis of a child presenting with encephalopathy following a viral prodrome. The incidence should continue to be monitored, if less intensively that via the BPSU. Methods of achieving this are currently under consideration, but in the meantime it is essential that such cases are considered as an adverse drug reaction to aspirin and reported to the Committee on Safety of Medicines via the "yellow card". This will reveal any upsurge in the event of an influenza epidemic which might require action in the form of public education, and will inform any re-evaluation by the regulatory authorities of the upper age limit on the warning.

Second - because the classic form of the illness has become so rare, it is now more likely that a patient presenting with a Reye's syndrome-like illness has an inherited metabolic disorder especially if the child is aged under three years (although these disorders can present in later childhood or even in adult life). All of the six cases reported in 1999/2000 and 2000/2001 for whom further information was provided were atypical for classic RS and five were under two years of age. Three of them subsequently



Annual Report (continued)

did have a revised diagnosis - to an inherited metabolic disorder in two. The observation that all reported cases in these last one and a half surveillance years had at least some investigations for inherited metabolic disorders and that numbers of reports of atypical cases have also declined in recent years, suggests that diagnostic awareness of these conditions has increased.

(ii) Work with the Medicines Control Agency

During 1999, anonymised data from the surveillance scheme were requested by the Medicines Control Agency for a paper to be put before the Committee on Safety of Medicines. This paper reviewed the case for increasing the age limit on the UK aspirin warning to include teenagers (as it does in the USA) and was partly prompted by the observation that, of 17 aspirin-associated cases reported since June 1986, 10 were aged over 12. The Committee on Safety of Medicines reached its decision in November 2000: it concluded that extension of the existing advice to include children aged 12 years and above "could not presently be justified".

This disappointing decision was challenged by Dr Hall in 2001. The outcome was that the Committee on Safety of Medicines reversed its decision. It sought further input from the Surveillance Scheme into the preparation of new cautionary advice on the use of aspirin in children under 16, which was recently published (April 2002).

(iii) Advisory support for the National Reye's Syndrome Foundation

Over the period under review, Dr Hall has advised the Honorary Administrator of the Foundation on a number of issues arising from correspondence received by him. These include a review of a grant application from the School of Biomedical Sciences, Queens Medical Centre, Nottingham to undertake laboratory studies into the causation of RS and an approach from an animal rights organisation. She also advised on the content of the Foundation's new website which was set up in 2001.

(iv) Professional Education

In the report for the year ending September 2000, mention was made of a proposal to organise a Workshop, to be fully funded by the Foundation. The principal goal of this workshop would be to set up an educational initiative to optimise the diagnosis and management of Reye-like childhood encephalopathies and of classic RS in the UK.

During the remainder of 2000 and in 2001, support for the Workshop was gained from the Executive Committee of the RCPCH and from the British Inherited Metabolic Disease Group (BIMDG - a professional association to which doctors and others in allied disciplines who specialise in these disorders belong). A Workshop Steering Group was convened. This consisted of Dr Hall, the Chair of the RCPCH Quality of Practice Committee and a consultant paediatrician specialising in inherited metabolic disorders and representing the BIMDG. Preliminary plans were drawn up at a meeting of the Group in April.



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(iv) Professional Education (continued)

At this time, Dr Hall obtained permission from the Foundation's Trustees to use part of the balance of her grant for running the surveillance scheme to support her in planning and organising the Workshop. This work included selecting and inviting participants, organising a suitable date and venue and preparing a briefing document. The latter consisted of a framework of questions about the diagnosis and management of RS and Reye-like disorders, which were to be allocated to individual participants according to their expertise. By the end of September 2001, a date (March 2002) and venue for the Workshop had been set, participants invited and the briefing document drafted.

Submitted by
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APPENDIX

BRITISH PAEDIATRIC SURVEILLANCE UNIT EXTRACT FROM 15th ANNUAL REPORT 2000 – 2001

Reye's syndrome

Key points

- * Surveillance of Reye's syndrome via the BPSU ceased in May 2001.
- * The "incidence of "classic" Reye's syndrome has dropped dramatically since June 1986.
- * Diagnostic vigilance, however, needs to be maintained, especially in the setting of an influenza epidemic.
- * Continued monitoring of classic, aspirin-associated Reye's syndrome is essential. Such cases should be treated as an adverse drug reaction and reported on a "yellow card" to the Committee on Safety of Medicines.
- * Most cases reported in recent years, although satisfying the diagnostic criteria, have been atypical.
- * It is essential to investigate fully, patients presenting with a Reye-like illness *or* with sudden death associated with cerebral oedema and fatty liver, for the relevant inherited metabolic disorders.

Background

Surveillance of Reye's syndrome began in August 1981 as a venture shared between the (then) British Paediatric Association and the Public Health Laboratory Service Communicable Disease Surveillance Centre (CDSC). Responsibility for case ascertainment was transferred to the BPSU in June 1986. The administration of the scheme was transferred from CDSC to the Department of Paediatrics at Sheffield in 1995.

In the early years, the surveillance data demonstrated that the incidence of Reye's syndrome in the British Isles was similar to that in the United States, where national surveillance of this condition has been in place since the mid-seventies. However, British and Irish cases occurred at a younger mean age, there was no clear seasonal (winter) peak, no striking association with influenza and chickenpox (although such cases did occur), and a higher case fatality rate.

In 1984/85 a risk factor study, mounted on to the surveillance database, showed an association between Reye's syndrome and consumption of aspirin. In response both to this and to similar findings in the United States, the Committee on Safety of Medicines issued public and professional warnings in 1986 about the use of aspirin in children. Since then, products that contain aspirin have been required to carry warning labels which state "Do not give to children under 12 except on the advice of a doctor". From April 1998, aspirin-containing medications are additionally required to state on patient information leaflets: "There is a possible association between aspirin and Reye's syndrome when given to children with a fever."



There is increasing recognition that a number of inherited metabolic disorders – most notably those affecting fat oxidation, amino acid metabolism and ureagenesis, may present as a 'Reye-like' illness, which is *clinically and pathologically indistinguishable from Reye's syndrome*. The surveillance questionnaire, although currently in its simplest and shortest format since 1981, therefore seeks information on whether patients have been investigated for these disorders.

In addition to BPSU reporting, cases are also ascertained via death entries provided by the Office for National Statistics, the General Register Office for Scotland, the Northern Ireland Statistics and Research Agency, and via laboratory reports to CDSC.

Objectives

To describe the epidemiological and clinical features of Reye's syndrome in the British Isles, to monitor long term trends, and to provide a database for detailed clinical, laboratory, and aetiological studies.

Study duration

June 1986 – April 2001.

Case definition

A child under 16 years old with:

- * *unexplained* non-inflammatory encephalopathy, and one or more of:
- * serum hepatic transaminases elevated to at least three times the upper limit of normal;
- * blood ammonia elevated to at least three times the upper limit of normal;
- * characteristic fatty infiltration of liver (biopsy or autopsy).

Since this definition is relatively non-specific, cases reported from surveillance year 1994/95 onwards, whose diagnosis has not been revised, have been allocated a "Reye's-score".¹ Because of the non-specificity of the case definition and because there may still be "Reye-like" inherited metabolic disorders as yet undiscovered, a case of Reye's syndrome can rarely, if ever, be described as confirmed; it is better designated as "compatible with" the diagnosis.

Study duration

Ascertainment of cases via the BPSU began in June 1986 and ended in April 2001.

Analysis

Between August 1981 and April 2001 a total of 632 suspected cases of Reye's syndrome were reported (Table 15), but the diagnosis was subsequently revised in 164 (26%). Eighty-one (49%) of the revisions were to one of the 'Reye-like' inherited metabolic disorders. Two hundred and thirty nine (53%) of the total 450 cases compatible with a diagnosis of Reye's syndrome died.



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In the year to July 31st, 2000, four reports of new cases were received and further information was provided on all of them.

One of the four diagnoses was later revised, leaving three patients whose clinical and pathological features were compatible with the case definition of Reye's syndrome. Three of the cases were first reported via the BPSU, one was ascertained only via a death entry. *In the period August 1st 2000 to April 30th 2001* three reports were received, further information was provided on two. One of the diagnoses was later revised; in the other case a specific alternative diagnosis was not reached, but an inherited metabolic disorder was so strongly suspected that Reye's syndrome was not recorded as a cause of death.

Cases compatible with a diagnosis of Reye's syndrome (surveillance year 1999/2000, N=3):

There was one male and two females, the ages were 2 months, 14 months and 23 months. Their illnesses were in November, January and April. All lived in England – there were no reports this year from Northern Ireland, Republic of Ireland, Wales or Scotland.

One child, whose investigations for an inherited metabolic disorder were negative, recovered completely. Of the two who succumbed, both died suddenly and unexpectedly during relatively mild viral-type upper respiratory and gastroenteritic illnesses respectively. The diagnosis of Reye's syndrome was made at autopsy on the basis of cerebral oedema and a characteristic histological appearance of the liver. Investigations on both for inherited metabolic disorders were negative. Virological investigations on all three cases were also negative. Only one patient had received preadmission medications paracetamol and ibuprofen.

The 'Reye Scores' (*possible range 1 - 25*) were 9,12 and 15. The median scores in the previous five years were 12,12,13,13 and 16 respectively.

Revised diagnosis cases

The one case in 1999/2000 was a nine month old boy who died suddenly during an episode of gastroenteritis. Although the autopsy findings led to a preliminary diagnosis of Reye's syndrome, subsequent investigations revealed medium chain acyl coA dehydrogenase deficiency. Of the two cases in 2000/2001, one was a two month old boy who died suddenly during an upper respiratory illness. An inherited metabolic disorder was suspected on grounds of extensive fatty change in liver, kidneys, heart and muscle, but investigations were negative. The other patient was a four year old girl presenting with encephalopathy and abnormal liver function tests after a gastroenteritic illness in whom the subsequent diagnosis was pneumococcal meningitis and cerebrovascular accident complicating sickle cell anaemia.

Comment

This Annual Report will be the last in the series which started in 1981/82, when surveillance of Reye's syndrome began. As the *first clinical reporting scheme* involving paediatricians in the UK and Ireland in the epidemiological surveillance of rare disorders of public health importance, *the Reye's syndrome surveillance scheme was the forerunner of the BPSU*. It is fitting that the total cases in the last complete surveillance year, three (none of whom had classic, aspirin associated Reye's syndrome), equals the lowest total recorded in 19 years and that, so far up to the end of surveillance in April 2001, there have been no cases at all. It is fitting because the trends vindicate the



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public health action taken on the use of aspirin in children in 1986 which, as also reported in the United States, represents a *triumph for primary prevention of a devastating childhood illness*.²

National surveillance of Reye's syndrome through paediatrician reporting has now ceased, but two important issues remain:

First – *classic, aspirin associated Reye's syndrome* has now become so rare that some clinicians have dismissed it as being no longer of any clinical importance. However, this is a dangerously complacent view of a disease capable of re-emergence during a major influenza epidemic or pandemic (it is now 10 years since the annual influenza incidence rose to epidemic levels and even these were not as high as in the last major epidemic in the 1970's) if aspirin warnings are disregarded or ignored because the child is over 12. The decline of Reye's syndrome means that a new generation of paediatricians in training and young consultants will certainly never have seen or heard about a case and are unlikely to have read about it or had it included in educational materials. Furthermore, it is likely to be under-recognised by physicians caring for teenagers and older adults with acute encephalopathy. Thus if there is a resurgence, the "old days" of late diagnosis, late or inappropriate treatment and poor outcome in terms of mortality and brain damaged survivors may be seen again.

It is, therefore, most important that Reye's syndrome is not forgotten or removed from the differential diagnosis of a child presenting with encephalopathy following a viral prodrome. The incidence should continue to be monitored, if less intensively than via the BPSU. Methods of achieving this are currently under consideration, but in the meantime it is *essential* that such cases are considered as an adverse drug reaction to aspirin and reported to the Committee on Safety of Medicines via the "yellow card". This will reveal any upsurge in the event of an influenza epidemic which might require action in the form of public education, and will inform any re-evaluation by the regulatory authorities of the upper age limit on the warning.³

Second – because the classic form of the illness has become so rare, it is now more likely that a patient presenting with a Reye's syndrome-like illness has an inherited metabolic disorder especially if the child is aged under three years (although these disorders can present in later childhood or even in adult life).⁴ All of the six cases reported in 1999/2000 and 2000/2001 for whom further information was provided were atypical for classic Reye's syndrome and five were under two years of age. Three of them subsequently did have a revised diagnosis – to an inherited metabolic disorder in two. The observation that all reported cases in these last one and a half surveillance years had at least some investigations for inherited metabolic disorders and that numbers of reports of atypical cases have also declined in recent years, suggests that diagnostic awareness of these conditions has increased.

We are most grateful to all paediatricians who, over the past 20 years, have reported cases and provided further information.

Funding

The Reye's syndrome surveillance scheme is funded by the National Reye's Syndrome Foundation of the UK, to whom the investigators are most grateful.



Table 15 *Reye's Syndrome Surveillance 1981/82 – 2000/01*⁺

Reporting period (August-July)	Total reports from the British Isles	Revised diagnosis (inherited metabolic disorder in brackets)		Cases of Reye's syndrome*	Number of deaths (of cases)
1981/82	47	7	(3)	40	26
1982/83	69	10	(6)	59	34
1983/84	93	12	(3)	81	36
1984/85	64	8	(2)	56	32
1985/86	53 ¹	13	(4)	39	22
1986/87	47	21	(11)	26	13
1987/88	44	12	(3)	32	19
1988/89	31	13	(6)	18	9
1989/90	24 ¹	8	(5)	15	7
1990/91	25	13	(8)	12	5
1991/92	23 ²	6	(5)	15	6
1992/93	21 ³	10	(6)	5	4
1993/94	20 ⁴	13	(7)	3	3
1994/95	17 ²	3	(2)	12	3
1995/96	18 ¹	2	(1)	15	7
1996/97	7	2	(2)	5	4
1997/98	11	4	(2)	7	5
1998/99	11	4	(3)	7	2
1999/00	4	1	(1)	3	2
2000/01	3 ⁺	2	(1)	0	0
TOTAL	632	164	(81)	450	239

* *Compatible with the diagnosis (see text)*

2 *Follow-up not received for two cases*

+ *to April 2001*

3 *Follow-up not received for five cases and one case did not meet the case definition*

1 *Follow-up not received for one case*

4 *Follow-up not received for five cases*

Note: *numbers may differ from previous versions of this table because of late ascertainment of cases and revised diagnosis.*

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