

## Chronic Fatigue Syndrome (CFS) and immunisation

### *What is chronic fatigue syndrome?*

Chronic fatigue syndrome (CFS) is the term generally accepted for the range of complaints commonly refer to as myalgic encephalomyelitis (ME) or chronic fatigue and immune dysfunction syndrome. CFS is characterised by persistent and unexplained fatigue resulting in severe impairment in daily functioning. Sporadic CFS-like cases and epidemics have been described since the 19th century. Researchers, practitioners, and patients have not been able to agree on the name (ME or CFS), on case definitions, on the acceptability of diagnosing CFS as an illness, on the absence of underlying pathophysiology and the need to continue research in somatic causes, or on the effectiveness of cognitive behaviour therapy (CBT). (1)

### **Clinical manifestations**

The main complaint of patients with CFS is persistent severe fatigue but most have concomitant symptoms. The most widely supported scientific case definition is the 1994 CDC definition that is now considered the standard. (1994 case definition for CFS from US Centers for Disease Control and Prevention). Characterised by persistent or relapsing unexplained chronic fatigue.

- Fatigue lasts for at least 6 months
- Fatigue is of new or definite onset
- Fatigue is not the result of an organic disease or of continuing exertion
- Fatigue is not alleviated by rest
- Fatigue results in a substantial reduction in previous occupational, educational, social, and personal activities
- Four or more of the following symptoms, concurrently present for at least 6 months:
  - impaired memory or concentration,
  - sore throat, tender cervical or axillary lymph nodes,
  - muscle pain,
  - pain in several joints,
  - new headaches,
  - unrefreshing sleep, or malaise after exertion

#### Exclusion criteria

- Medical condition explaining fatigue
- Major depressive disorder (psychotic features) or bipolar disorder
- Schizophrenia, dementia, or delusional disorder
- Anorexia nervosa, bulimia nervosa
- Alcohol or substance abuse
- Severe obesity(1)

### **Epidemiology**

Studies using the definition above found prevalence's among adults of 0.18% to 0.42% with rates being higher in women, minority groups, and lower educational and occupational status. The prevalence is much lower among children and adolescents than among adults. Full recovery without treatment is rare. (1)

### **Aetiology**

Explanations for CFS have been sought in many areas and only a few have yielded abnormalities. The aetiology and pathogenesis are believed to be multifactorial and one or more factors in each

category are conditional but insufficient for development of CFS. Factors are predisposing (such as personality and lifestyle) precipitating (such as stress, infection or infectious mononucleosis) and perpetuating factors (such as avoidance of physical activity). (1)

## Treatment

To date systematic reviews have found only Cognitive Behavioural Therapy (CBT) and graded exercise therapy (GET) to be beneficial. (1)

## Vaccination and chronic fatigue

There have been suggestions that vaccines have an involvement in chronic fatigue. As with many diseases of unknown origin, immunisation have been investigated as a possible cause. In particular, hepatitis B vaccine and an Outer Membrane Vesicle (OMV) Meningococcal Vaccine.

### Hepatitis B vaccine and CFS

The concern that CFS is linked to Hepatitis B vaccine started in October 1990 in Canada following a television programme where a nurse alleged she developed CFS after receipt of the vaccine. After this programme, 69 people reported similar experience. The CDC investigated these reports and concluded there was no evidence for any link for the following reasons:

The case series consisted of self reporting individuals and it is known that health care workers have always made up the majority of cases seen at CFS clinics before Hepatitis B vaccine was licensed. Only 31 cases satisfied the criteria for CFS.

A study of 700 health care students did not show any evidence of CFS.

- There was no dose-response relationship reported.
  - A matched case-control study found only 10/134 patients had a history of Hepatitis B virus (HBV) infection before onset of CFS. This Hepatitis B vaccination status is similar to that of the general population.
  - Lack of biological plausibility - Chronic fatigue or tiredness is not one of the common symptoms among chronically infected HBV carriers without chronic liver inflammation.
  - Lack of consistency - CFS is a disease that is investigated by many researchers globally and no reports of similar alleged association with HBV vaccine have been otherwise identified.
- (2,3)

**It was concluded that evidence linking CFS to HBV vaccination largely consists of data generated from publicity.**

### OMV Meningococcal Vaccine and CFS

During 1980s Norwegian clinical trials of an outer membrane vesicle meningococcal vaccine there was one case of CFS reported in the 149,000 vaccinees. This was not considered to be caused by the vaccine.

New Zealand's MeNZB™ vaccine was based on the Norwegian vaccine. When New Zealand introduced the MeNZB™ vaccine years later, it was noted on the data sheet that CFS was a possible rare side effect of the vaccine, although to date no causal link has been made.

To date, no cases of cases of chronic fatigue associated with MeNZB™ are recorded on the Centre for Adverse Reactions Monitoring database in New Zealand, the place where this would be expected to be recorded.

### Influenza vaccine and CFS

A review investigating whether influenza vaccine worsened existing CFS symptoms concluded that: influenza immunisation appears to provide protective antibody levels without worsening CFS symptoms or causing excessive adverse effects (4).

## ***Balance of evidence***

**At this time there is no evidence to support vaccines as a cause of CFS.**

## **New Zealand Issues**

### ***Anticipating coincidental events***

It is possible to predict how often one would expect to see a coincidental association between a health event and immunisation. Using the expected incidence (number of cases per population to be vaccinated per time period) of the health event. For example, assume that one million children aged 6 weeks-20 years are immunised in a mass campaign and the background illness rate for this condition in this population is 3 per 100,000 per year. Then, 7.5 cases can be expected in the month after immunisation, simply by coincidence and 90 cases in the year. These cases will be temporally associated (similar timing) with, even though entirely unrelated to, immunisation.

### **How is a new vaccine monitored for any unforeseen side effects?**

The introduction of MeNZB™ was supported by research data from a number of countries over many years. When most of the population is given a vaccine, events will occur following the receipt of the vaccine that are coincidental. The comprehensive Meningococcal B Vaccine (MeNZB™) Safety Monitoring Plan enables us to determine what is coincidental and what could be attributable to the vaccine.

Vaccine safety is paramount and the NZ system is designed to detect any potential problems and investigate them in detail to establish causality.

New Zealand instituted a gold standard in safety monitoring for a new vaccine. This included the Spontaneous Reporting Programme, where GPs voluntarily reported reactions they thought may be related to the vaccine as they do with all medicines and vaccines, and the Intensive Vaccine Monitoring Programme (IVMP), where a smaller group of general practices were intensively monitored and all reports of any reactions or illnesses were considered for up to six weeks after vaccination, whether or not they thought they were related to the vaccine.

In the early stages there was also hospital based monitoring which meant that any child in the first area of roll out who went into hospital with any condition that could be remotely or possibly related to a vaccine was very carefully assessed. The Intensive Monitoring System did not pick up any increase in hospital visits for any monitored condition which included immunological and neurological conditions.

There has been no increase in the incidence of monitored conditions since the programme started. These are conditions that occur every year in a small number of children. As expected, these conditions continued to present during the programme, both in children who received the vaccine and children who did not receive the vaccine. The rates of these conditions did not increase

### **Independent Safety Monitoring Board**

The Independent Safety Monitoring Board (ISMB), a panel of international and New Zealand experts established by the Health Research Council of New Zealand (HRC), reviewed safety data throughout the programme until the end of June, 2006.

The ISMB said it was satisfied that there was an "outstanding programme of sensitive and objective safety monitoring" throughout the rollout of the MeNZB™ vaccine.

The ISMB also advised that it found no evidence of any significant adverse health event associated with the vaccine.

With the end of the mass immunisation campaign, the monitoring of adverse events following MeNZB™ is now the same as for other vaccines.

Health professionals will continue to report any adverse events to the Centre for Adverse Reactions Monitoring (CARM) which monitors MeNZB™ and routine schedule vaccinations.

It was important to have a comprehensive safety surveillance system to identify serious adverse events that could be truly related to vaccination and to ensure that allegations relating to vaccine safety could be rapidly investigated.

## **Meningococcal B Vaccine (MeNZB™) Safety Monitoring Plan**

The Meningococcal B Vaccine (MeNZB™) Safety Monitoring Plan includes an outline for additional investigations that may be required over time. These include investigations of conditions not previously identified as being related to vaccination, conditions that may appear some years after vaccination or conditions that may not in the first instance be diagnosed at a hospital.

The plan also gives consideration to investigation of events for which there have been high profile allegations of an association with vaccination, despite lack of supporting scientific evidence, for example, autism, chronic fatigue syndrome, and attention deficit hyperactivity disorder. None of these conditions have been linked to MeNZB™.

The key to investigations of events that take a long time to develop is the ability to identify everyone who has received the vaccine. New Zealand is well placed to do this as the NZ Meningococcal B Immunisation Programme requires that all MeNZB™ vaccinations are recorded on the National Immunisation Register.

The Meningococcal B Vaccine (MeNZB™) Safety Monitoring Plan is available at:

<http://www.moh.govt.nz/moh.nsf/by+unid/EE16A62E34DF2B07CC2571FB0079A5C3?Open>

This plan was used to guide the implementation of several complementary monitoring systems, analysis of data generated from these checks and assessment of data by the ISMB.

## **Ethics and MeNZB™**

### ***Was it ethical to introduce the MeNZB™ vaccine to the New Zealand population?***

The MeNZB™ vaccine was introduced after careful examination of its efficacy, its cost/benefit and risk/benefit ratio and against the backdrop of unacceptable levels of meningococcal B invasive disease. New Zealand's rates of all meningococcal diseases were 14.9 per 100'000 in 2002 prior to the introduction of the vaccine; Australia introduced a vaccine when rates were 3.6 per 100,000. It would have been unethical for New Zealand's Ministry of Health not to introduce a vaccination programme.

Another consideration when introducing a new public health intervention is that there is sufficient societal support for those who claim an association between the vaccine and possible side-effects (5). There were a range of places that members of the New Zealand public could go to get more information about the vaccination programme, including the Ministry of Health, Immunisation Advisory Centre and their local primary care provider. The negligible risk of rare adverse events has been debated openly in the media. Moreover, the datasheet included all adverse events reported during the trials of the Norwegian parent vaccine. This, of course, included the case of one report of chronic fatigue syndrome. This, however, does not imply a causal association.

The benefit of having a low probability of getting meningococcal B invasive disease post-vaccination would outweigh the minor risk of getting some of the common side effect and occasionally, rare adverse events. The probability of getting the disease is greater than getting an adverse event. It is important not to give the wrong significance to the probable impossibility of

attaining complete certainty about immunisation (6). Rather, it is more useful to consider the climate for introducing a vaccine and the overall benefits of this introduction to the population

## In summary

**The existing literature and clinical trial results show no association between chronic fatigue syndrome and any vaccine, including MeNZB™.**

### References

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