June 14 2006

Mr Elton Humphery
Committee Secretary
Senate Community Affairs References Committee
Suite S1 59
Parliament House
Canberra ACT 2600

Dear Secretary,

As part of the Senate Community Affairs References Committee inquiry into gynaecological cancer in Australia, I am delighted to present the following submission to the Committee on behalf of CSL Limited.

CSL Limited believes in the importance and significance of this inquiry, and moreover, the many issues associated with cervical cancer are well understood by CSL Limited. With this in mind, and in order to more fully contribute to the inquiry and the discussion around gynaecological cancers in Australia, CSL would greatly appreciate the opportunity to appear before the Committee at a public hearing during the course of the inquiry.

If you have any further queries regarding the submission or CSLs offer to appear before the Committee, please don't hesitate to contact me. My details are below.

Kind regards,

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Submission to the Senate Community Affairs References Committee
Inquiry into gynaecological cancer in Australia

Prepared by Dr. Rachel David, CSL Limited

14 June 2006

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Summary

The Australian Institute of Health & Welfare reports that with the expected ageing of the population, the overall number of new cases of gynaecological cancers is projected to increase by 15 percent from 3,886 in 2001 to 4,488 in 2011, with a 95% prediction interval from 4,048 to 5,191 (AIHW, 2004).

Within the total incidence of gynaecological cancers in Australia, each year over 800 women are diagnosed with a form of cervical cancer that requires treatment involving surgery, chemotherapy and/or radiotherapy.

In addition, approximately eighteen thousand women are diagnosed annually with low-grade cervical abnormalities requiring further follow-up and/or investigation. Fifteen thousand women will have high grade cervical abnormalities detected which require surgery to remove the affected part of their cervix.

These figures equate to forty Australian women a day requiring surgery to remove pre-cancerous or cancerous cervical lesions. Procedures to remove pre-cancerous lesions can have adverse effects on the ability to carry a child to term. Eighty percent of these high-grade lesions occur in women under the age of forty.

Cervical screening detects approximately 100,000 abnormal pap smears annually (NHMRC, 2005). These women require more frequent testing, resulting in feelings of stress and anxiety whilst waiting for a definitive diagnosis and significant health care costs.

Whilst there is little doubt that regular Pap smears are effective in detecting abnormalities and/or pre-cancerous lesions and that the national screening program has been successful in reducing the number of cases of invasive cancer, screening does not prevent the disease.

Our current national screening program is considered a success, but despite this, cervical cancer continues to claim the lives of approximately 230 Australian women each year.

Human Papillomavirus (HPV) is the first ever identified "necessary cause" of a human cancer, and is considered responsible for more than 99.7 percent of cervical cancers (Walboomer et al, 1999). Up to 70 percent of sexually active women will become infected with at least one HPV type in their lifetime (Bosch et al, 2003).

We are about to enter an era where a vaccine specifically designed to prevent cervical cancer will be available. GARDASIL (Quadrivalent Human Papillomavirus Types 6,11,16,18 Recombinant Vaccine) is a quadrivalent vaccine targeting four human papillomavirus (HPV) types 6, 11, 16 and 18, and will soon be available to the Australian public.

The vaccine types in this vaccine, 6, 11, 16 and 18, are the most common types affecting women's health, accounting for 70 percent of cervical cancer cases and a significant proportion of cervical abnormalities.

In clinical trials of most sexually active 16 to 26 year old women, GARDASIL prevented 100% of high grade cervical pre-cancers and non-invasive cancers (CIN 2/3 and AIS) associated with HPV types 16 and 18. (The Lancet, 2005).

Clinical data shows that this vaccine prevents pre-cancerous abnormalities due to the vaccine HPV types and thus can provide protection against cervical cancer. This will be the first opportunity to provide primary prevention of cervical cancer and other HPV-related diseases.

With regard to the Committee's terms of reference, the widespread availability of a preventive vaccine for cervical cancer will provide;

- benefits to Australian women through reduced morbidity and mortality associated with cervical cancer and associated pre-cancerous disease;
- benefit to the Australian community through a reduction in health care costs and greater productivity resulting from a healthier community;

- improved health outcomes to women in rural and remote regions of Australia through accessible primary prevention for cervical cancer and associated pre-cancerous disease;
- improved health outcomes for Aboriginal and Torres Strait Islander women through accessible primary prevention for cervical cancer and associated pre-cancerous disease;
- an opportunity to use routine vaccination to improve awareness of cervical cancer and associated risk factors;
- a complementary strategy to screening and early detection programs.

Pivotal to attaining these outcomes will be to ensure that access to the vaccine is universally available to provide the greatest benefit. It is recommended that the Australian Government expedite the use of this vaccine on a population wide basis via the national immunisation program which has been highly effective in delivering high vaccination coverage and significantly reducing the incidence of vaccine preventable disease.

It will also be important that the current Pharmaceutical Benefits Advisory Committee (PBAC) process for assessing vaccines adopts an appropriate assessment methodology for considering preventive technologies as opposed to treatment and therapies for those persons with illness. Failure to adequately assess all direct and indirect benefits could jeopardise universal access to HPV vaccine.

Cervical cancer epidemiology

Cervical cancer causes significant morbidity and mortality in Australia:

Worldwide, cervical cancer rates are high with 500,000 new cases reported annually, 83 percent of which occur in developing countries. As a result, many countries including Australia have implemented regular Pap test screening programs to detect cervical abnormalities.

The Australian National Cervical Screening Program (NSCP) screens about 2 million women each year and reports approximately 100,000 abnormal Pap smears annually (NHMRC, 2005).

In 2003, high-grade pre-cancerous lesions were detected (on histology) in about 15,000 women. Low-grade abnormalities were detected (on histology) in a further 18,500 women (Bloomfield et all, 2005).

Each year, the National Cervical Screening Program detects over 800 new cases of invasive cervical cancer, and cervical cancer accounts for about 230 deaths annually. When compared to other cancers, cervical cancer has the youngest age at first diagnosis (53 years old) versus breast cancer (60 years), ovarian (63 years) and colorectal (70 years) cancer (ibid).

Cervical abnormalities affect young women and often results in surgical treatment:

Of the 15,000 women in whom, high-grade abnormalities were detected in 2003, about 80 percent were under 40 years of age (AIHW, 2005). Often these lesions require surgical treatment that involves removing part of or in some cases the entire cervix.

Treatments for removing cervical lesions include laser treatment, loop-electro-excisional procedure (LEEP), cryosurgery (cold coagulation), electrodiathermy, and cone biopsy (either by laser or by scalpel). In a small number of cases, a hysterectomy may be necessary. Every day, about 40 Australian women undergo such surgery.

Cervical cancer impacts significantly on women, in a significant number of cases in their childbearing years. Additionally, procedures to remove pre-cancerous lesions may also negatively affect the ability of a woman to carry a pregnancy to term.

Cervical cancer disproportionately affects indigenous communities:

While cervical cancer screening programs have largely been successful in reducing the mortality and morbidity rates associated with cervical cancer in Australia, evidence indicates that indigenous populations have been left behind.

Cervical cancer is still the leading cause of death in Aboriginal and Torres Strait Islander women in Australia (while it is the eighth most common cause of death for Australian women overall), and their risk of dying from cervical cancer is more than 10 fold that of non-Indigenous women.

These figures are alarming, as cervical cancer is one of the most preventable forms of cancer. Moreover, the data highlights the most serious limitations associated with current strategies to address cervical cancer – the lack of access to, and reach of, screening programs in regional, rural and indigenous communities.

In addition to the more recognisable burdens of morbidity and mortality associated with the disease, the psychosocial and economic burdens are significant and warrant attention also.

The psychosocial impact of current approaches to early detection of cervical cancer:

Pap testing is often a cause of deep anxiety for women, and even more so for those in whom an abnormality is detected and further investigation is required to establish a definitive diagnosis. If cancerous or precancerous lesions are confirmed, further stress and fear can result.

Following diagnosis, some women report difficulties coping with work, caring for their families, some may experience depression, self-blame, anger and moreover, often after treatment is administered, patients can develop psychosocial concerns that may lead to sexual dysfunction or issues with sexuality (Frazer et al, 2006).

Human Papillomavirus (HPV) and the causal link to cervical cancer:

Human Papillomavirus (HPV) is the first ever identified "necessary cause" of a human cancer, and is considered responsible for more than 99.7 percent of cervical cancers (Walboomers et al, 1999). Up to 70 percent of sexually active women will become infected with at least one HPV type in their lifetime (Bosch et al, 2003).

HPV types are classified as either high-risk or low-risk according to their propensity to cause malignancy. Not all types are oncogenic. Of the 100 types of HPV identified in humans, more than 40 infect the anogenital mucosa (Schiffman et al, 2003).

Of these, 15 types are high-risk and these are responsible for virtually all cervical cancers and most high-grade squamous intraepithelial lesions (HSIL) (Walboomers et al, 1999). Low-risk HPV types or non-oncogenic types rarely progress to neoplasia, but also cause significant disease such as anogenital warts, recurrent respiratory papillomatosis, and some low-grade squamous intraepithelial lesions (LSIL) (Clifford et al, 2005).

In summary HPV is associated with:

- 99.7% of cervical cancers;
- 50% of vulval, vaginal and penile cancers;
- 85% of anal cancers;
- 20% of oropharyngeal cancers;
- 10% of cancers of larynx and aerodigestive tract[2]recurrent respiratory papillomatosis; and
- >90% of all genital warts.

HPV types 16 and 18 cause 70 percent of cervical cancer and 50 percent of high-grade cervical abnormalities. HPV types 6 and 11 cause 90 percent of genital warts (von Krogh, 2001) and 10 percent of low-grade cervical abnormalities (Clifford et al, 2005).

HPV is usually transmitted by sexual contact, commonly through sexual intercourse. There are limited ways to prevent its transmission. Other ways to transmit HPV include vertical transmission (from mother to new born baby) and via contact with fomites such as undergarments and surgical gloves, although these routes of transmission are rare and not well documented.

Although other co-factors are thought to be required, cervical cancer does not develop without persistent high-risk HPV DNA in cervical epithelial tissue.

Prevention of cervical cancer can be achieved through prevention and control of genital infection with oncogenic HPV types. A vaccine to prevent HPV strains 16 and 18 as well as 6 and 11 has been developed. The basis of this vaccine, virus like particles, was the result of collaborative work between CSL and Professor Ian Frazer of the University of Queensland, in the early 1990's.

In clinical trials of mostly sexually active, 16 to 20 year old women, GARDASIL, prevented 100 percent of high-grade cervical pre-cancer and non-invasive cancers (CIN 2/3 and AIS) associated with HPV types 16 and 18 (The Lancet, 2005).

In light of this, it is indeed possible to prevent many cases of cervical cancer through vaccination, as HPV is a virus susceptible to immune attack. A vaccine proven to prevent the relevant HPV infection and growth of pre-cancerous lesions can therefore provide protection against invasive cervical cancer.

The promise of primary prevention:

Quadrivalent HPV vaccine targets HPV types 16 and 18 (responsible for 70 percent of cervical cancer and 50 percent of high-grade cervical abnormalities) as well as 6 and 11(that cause 90 percent of genital warts and 10 percent of low-grade cervical abnormalities).

As the HPV quadrivalent vaccine is a primary form of prevention (in that it intends to reduce the incidence of an illness in a population which is yet unaffected by the virus which causes the disease), high uptake of the vaccine will potentially reduce costs associated with mortality and morbidity caused by cervical cancer, and also minimise the number of abnormal Pap results and moreover the resulting adverse consequences such as further testing, surgery and psychosocial effects that occur subsequently.

Although screening programs have been largely successful in reducing the number of deaths attributed to cervical cancer through early detection, there are obvious limitations to the current screening process, namely:

- False negative results, false positive results, and limited sensitivity;
- Errors of interpretation of the smear;
- Inaccessibility of certain areas of the cervix;
- Less effective at detecting adenocarcinoma;
- Participation is never 100%, with only 60% of the target population having Pap tests within the two-year audit window (2002-2003) (AIHW, 2004);
- Lack of awareness, willingness and access for indigenous women;
- Many women don't maintain regular screening.

A universal vaccination program will not replace the need for a national screening program, and the two programs will be complementary, however, it is probable that screening requirements for vaccinated women will most likely alter in terms of the recommended age for commencement of screening and the interval between Pap tests.

There are a number of issues related to access to the spectrum of health services related to cervical cancer - screening, diagnosis, treatment and care, suitably qualified health professionals - that have a direct impact on cervical cancer morbidity and mortality.

Importantly, adding a national vaccination program with screening/early detection programs will significantly reduce the disease burden in Indigenous and non-English speaking background communities, where both the technical limitations and sub-optimal reach of the existing screening program are most apparent.

Access to immunisation programs/services for these sub-populations is potentially much greater than specialist procedural services.

<u>Universal access to HPV vaccine is important:</u>

The epidemiology of HPV infection and the available clinical trial data on HPV quadrivalent vaccine supports routine vaccination of females before they become sexually active (aged 11-12 years) for maximum public health benefit based on modeling showing more impact with routine vaccination.

A school-based program via the national immunisation program would result in vaccination of more females before sexual debut resulting in greater prevention impact. Implementation of a three-dose schedule at this age is also aided by the fact that other vaccines are recommended and provided routinely at this age.

In an Australian survey, 54 percent of mothers said they were extremely likey, 21 percent very likely and 10 percent somewhat likely to have their daughters vaccinated with quadrivalent HPV vaccine in a schools-based vaccination program (ANOP, 2004).

Immunisation with quadrivalent HPV vaccine will also offer benefits to older girls and women. Additionally, sexually active women should not be discouraged from vaccination. Even if a woman has been infected with one vaccine type, she will still benefit from protection against disease caused by the other three types.

Once approved by the Therapeutic Goods Administration (TGA), HPV quadrivalent vaccine is expected to be considered for government subsidy by the Pharmaceutical Benefit Advisory Committee (PBAC).

This process for listing vaccines has recently replaced the previous role undertaken by an expert vaccines committee, the Australian Technical Advisory Group on Immunisation. It will be important that the new function given to the PBAC for assessing vaccines is associated with the use of appropriate methodologies for considering preventive therapies as opposed to assessing treatments and therapies for existing illnesses.

A failure to adequately consider the health economics of a preventive vaccine for HPV and cervical cancer risks foregoing benefit to all Australian women and the community more broadly.

Summary of recommendation to the Inquiry

The availability of an effective HPV quadrivalent vaccine represents a revolutionary advancement for further significant reduction of the incidence of cervical cancer in Australia. In essence, cervical cancer caused by HPV types 16 and 18 (which account for approximately 70 percent of cervical cancers) will soon be a vaccine preventable disease. The most effective way of ensuring this assertion becomes a reality is to ensure this vaccine is accessible to all women.

Current screening programs, whilst effective, have limitations and do not prevent all cervical cancer. The National Screening Program has resulted in reduced rates of cervical cancer, however, Indigenous women and women from non-English speaking backgrounds have not experienced the same degree of decline in disease incidence.

The availability of a population wide HPV quadrivalent vaccine immunisation program for pre-adolescent girls to be delivered routinely via a school-based program under the National Immunisation Program should be expedited.

In addition, substantial benefit would be achieved from a catch-up vaccination program for females aged from 13 – 17 years.

The development and implementation of HPV quadrivalent vaccination programs provides and opportunity to review best practice guidelines for cervical cancer prevention in Australia.

It is hoped that the Senate inquiry into gynaecological cancers in Australia will highlight;

- the continuing significant morbidity and mortality associated with cervical cancer in Australia;
- the disproportionate and unacceptable incidence of cervical cancer in Indigenous women and women from non-English speaking background;
- the causal link between HPV infection and development of HPV related disease including cervical cancer;
- the impending availability of an effective preventive quadrivalent HPV vaccine; and
- the need to ensure universal access to those groups for whom the vaccine has the greatest benefit.

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