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Communicable Diseases Intelligence

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Contents:

VIRUS REPORTING SCHEME: A total of 1 428 reports were processed for this period.

Twenty two cases of Q fever were reported, one from Western Australia, two from South Australia, four from New South Wales, five from Victoria, and ten from Queensland. Occupational exposure data were available for:

- one South Australian case, a 19 year old male abattoir worker from Adelaide, and
- three Queensland cases, a 26 year old male meatworker from Brisbane, a 27 year old male station hand from Roma, and a 33 year old male shearer from Warwick.

None of the twenty two patients was involved in the Q fever vaccine field trial conducted in South Australia.

Adenovirus (typing in progress) was isolated from the nasal aspirate of a 3 year old male who died of dehydration following severe gastroenteritis and diarrhoea. No adenovirus or rotavirus was detected in the faeces.

Cytomegalovirus specific IgM antibody was detected in the serum of a 6 year old female with acute lymphoblastic leukaemia (ALL), who presented with a 3-week history of prolonged fever and severe jaundice. The patient had three recent blood transfusions but was serologically was negative for HBsAg, HAV and EBV.

Cytomegalovirus was isolated from :-

- the post-mortem tissues derived from the thyroid gland of a 43 year old male AIDS patient who died of cerebral toxoplasmosis;

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- the post-mortem tissues derived from the lungs, liver, kidney, duodenum, colon, thyroid, adrenal and prostate glands of a 35 year old male AIDS patient who died of Pneumocystis carinii pneumonia; and
- the saliva of a HIV-antibody positive male haemophiliac of unknown age.

MENINGOCOCCAL MENINGITIS OUTBREAK - SAUDI ARABIA

Neisseria meningitidis serogroup A outbreaks have been reported (August 1987) in three Saudi Arabian cities. The two holy cities of Mecca (Makkah) and Medina, and the city of Jeddah. Although the total number of deaths is not yet known, two of seven adults recently returned to England from pilgrimages to Mecca have died(1). Two children who were household contacts of recently returned pilgrims also developed infection(2).

In addition, since 9 August 1987 two definite and three probable cases of meningococcal disease have been reported among 1,250 pilgrims returning to the United States from Mecca and Medina. Onset of symptoms has been within 4 days of return to the United States. An additional traveller, who was not a pilgrim, was hospitalised recently with serogroup A meningococcal meningitis 4 days following her return to the United States. This woman had not travelled to Mecca and Medina, but had spent 5 weeks in Jeddah, where she had reportedly had some contact with pilgrims. Pilgrims returning on all recent direct flights from Jeddah to New York (Aug 18,20 and 25) received prophylaxis with rifampin at the New York Airport(3).

Australians intending to travel to Mecca or Jeddah, in particular those who may be living in overcrowded conditions or who may be involved in health care, should consider obtaining the bivalent A/C meningococcal meningitis vaccine (Mencevax (R) AC - Smith Kline & French) from the Commonwealth Serum Laboratories (Contact Mr David Murphy (03) 389 1276).

REFERENCES

1. Departmental Communication (Austr. Trade Comm., Jeddah)
2. CDR (1987) 33 : 1
3. MMWR (1987) 36 : 559

AIDS SURVEILLANCE - AUSTRALIA

To 30 August 1987, 583 cases of AIDS fulfilling the criteria of case definition have been reported to the National Health and Medical Research Unit in AIDS Epidemiology and Clinical Research. The distribution of those patients by State or Territory of notification (Table 1), by age group (Table 2), by risk category (Table 3) and by clinical presentation (Table 4) are shown below:-

TABLE 1: AIDS patients by State or Territory of Notification

STATE/ TERRITORY	CASES			DEATHS		
	Male	Female	Total	Male	Female	Total
NSW	383	15	398	216	13	229
VIC	95	1	96	40	1	41
QLD	39	3	42	28	2	30
WA	26	2	28	11	1	12
SA	10	1	11	2	1	3
NT	2	-	2	1	-	1
TAS	1	1	2	1	-	1
ACT	4	-	4	2	-	2
	560	23	583	301	18	319

TABLE 2: AIDS patients by age group

AGE (YEARS)	CASES			DEATHS		
	Male	Female	Total	Male	Female	Total
0 - 9	6	1	7	5	1	6
10 - 19	3	1	4	3	1	4
20 - 29	121	5	126	63	2	65
30 - 39	236	2	238	120	1	121
40 - 49	139	4	143	73	3	76
50 - 59	45	4	49	29	4	33
60 +	10	6	16	8	6	14
	560	23	583	301	18	319

TABLE 3: AIDS patients by risk category

RISK GROUP	CASES	DEATHS
Homo-/Bi-sexual	507	265
IV drug abuser	3	2
Homo-/Bi-sexual IV drug abuser	18	10
Blood transfusion recipient	37	32
Person with haemophilia	6	4
Heterosexual transmission	4	1
None of the above	8	5
	583	319

TABLE 4: AIDS patients by clinical presentation

INITIAL DISEASE REPORTED	CASES	DEATHS
Opportunistic infection (incl. PCP)	429	242
Kaposi's sarcoma (KS) alone	108	50
KS + Opportunistic infection	19	13
Lymphoma	22	11
Lymphoma and Opportunistic infection	5	3
	583	319

AIDS - DRUGS USED FOR TREATMENT
(Part I - AIDS Review Series)
Introduction

Chemotherapeutic approaches for the control of human immunodeficiency virus (HIV) infection have attracted considerable attention since the recognition of this retrovirus as the aetiological agent of acquired immunodeficiency syndrome (AIDS). This review gives an update on antiviral agents used for HIV treatment.

There are a number of stages in the replicative cycle of HIV which can be targeted for action by antiviral agents.

STAGE 1

. Adsorption or penetration: HIV begins replication by binding of the envelope glycoprotein to specific cell receptors of CD4+ target cells. The virus fuses with the cell membrane, penetrates the cell, and is subsequently uncoated, with the release of its genomic RNA.

. One of the strategies for novel antiviral drugs has developed from recent demonstrations that infection by a virus requires the presence of an active site on the viral membrane that binds to a receptor on the host cell membrane. Interference with this binding process has recently been demonstrated to reduce viral infectivity. AL-721[1] and Peptide T[2] have been reported to have activity against viral attachment or penetration, but these reports need confirmation.

1. AL-721 is a novel lipid compound that is composed of neutral glycerides, phosphatidylcholine, and phosphatidylethanolamine in a 7:2:1 ratio, and has a demonstrated ability to extract cholesterol from cellular membranes both in-vivo and in-vitro[3]. Results obtained with H9 cell lines (immortalised helper T-cell line) infected with HIV demonstrated the virucidal effects of AL-721 against HIV[4]. In preliminary trials in human subjects, the administration of a daily 10 to 15 g of AL-721 (producing an in-vivo concentration above 1mg per mL) restored diminished lymphocyte proliferative capacity in normal elderly patients. These daily oral doses of AL-721, a yellow oily liquid, appeared to be well tolerated, and no adverse effects were observed during a six-week course of treatment.

   Unpublished studies of open trials, involving 16 AIDS patients in Israel and 8 patients with HIV-related persistent generalised lymphadenopathy in New York, gave promising results.

2. Peptide T D-Ala-Ser-Thr-Thr-Thr-Asn-Tyr-Thr-NH_2 is an octapeptide which offers a novel approach to the therapy of AIDS by inhibiting the binding of HIV to lymphocytes.

   Researchers at the National Institute of Mental Health (NIMH-USA) reported that only the final five amino acids are required for biological activity. This group, using an

undefined strain of HIV virus and fresh peripheral blood lymphocytes, reported that peptide T inhibited HIV replication in-vitro. Five other research groups have been unable to reproduce this result.

Despite this controversy Swedish researchers have reported that preliminary clinical studies in four AIDS patients, using intravenous doses of 2-4 mg/day for four weeks, have shown beneficial effects on lymphocyte counts, some of which returned to normal. A further study, in 40 patients is being planned.

STAGE 2

. Reverse transcription: In the cytoplasm, the viral genomic RNA is transcribed into DNA by the virus-encoded reverse transcriptase enzyme, a target for many antiretroviral drugs.

The classical approach to controlling viral infection, including HIV, is the use of nucleoside analogues to inhibit this viral reverse transcriptase enzyme.

A. The following antiviral agents are members of the broad family of 2',3'-dideoxynucleoside analogues which include:

1. AZT (Azidothymidine-Zidovudine-Retrovir)

AZT is a synthetic thymidine analogue in which the 3'-hydroxy group of thymidine is replaced by an azido group. When AZT is intracellularly phosphorylated (ie when AZT is incorporated into DNA by HIV DNA polymerase/reverse transcriptase), the azido group (the 3'substitution) blocks the formation of the 5'→ 3' phosphodiester bond, thereby terminating the DNA chain prematurely(6).

AZT is approximately 100 times more effective a substrate for reactions catalysed by HIV reverse transcriptase than those catalysed by cellular DNA polymerase of mammalian cells(7). Despite this extraordinary selectivity, chronic administration of AZT has been associated with anaemia and leucopenia severe enough for more than 50% of long-term AZT-treated patients to become transfusion dependent and for a considerable number of these to have to discontinue treatment because of severe bone marrow toxicity(8).

Although there is insufficient clinical experience with AZT to exclude the possibility that the doses of AZT required, when it is given singly, may have toxic effects on other tissues with a high cell turnover, it has been concluded that AZT appears to be at least temporarily effective in decreasing mortality and morbidity in some patients with AIDS or AIDS-related complex (ARC)(9). How long drug treatment can be continued is unknown since bone marrow toxicity can be severe. Available data are insufficient to judge which patients will have the most favourable ratio of benefit to risk.

2. DDC (2'3'-dideoxycytidine) is a synthetic cytidine analogue which the U.S. government has applied for a patent and given the pharmaceuticals company Hoffman LaRoche an exclusive licence to manufacture.

Preliminary studies suggest that DDC is phosphorylated by cellular kinases to a triphosphate form that inhibits HIV reverse transcriptase. These effects can be reversed by the addition of deoxycytidine, probably by competition for deoxycytidine kinase(10).

Currently there is no data to compare the efficacy and safety of DDC with AZT. However, in the laboratory, DDC halts the replication of HIV at about one-tenth of the dose required with AZT.

DDC, which could be the next nucleoside analogue to become available for treatment, is currently at phase 1 clinical trial stage.

These studies, are being conducted at:

. John Hopkins where patients are receiving 0.03-10 mg/kg body weight daily, and
. Standford University where patients with AIDS and AIDS-related complex are receiving similar doses.

No results of these tests are yet available(11).

3. CNT (Cyanodideoxythimidine), another thymidine analogue closely related to AZT, is a new nucleoside analogue which the U.S. government is currently pressing the pharmaceuticals industry to manufacture and test.

Researchers are still experimenting with this nucleoside analogue, by culturing lymphocytes exposed to HIV in the presence of CNT. Preliminary observations indicate that CNT, even in very small quantities, is effective against HIV, leading the laboratory to comment that CNT appears more effective than AZT. No animal testing of CNT has yet started but researchers commented that, milligram for milligram, CNT appears more effective than AZT against HIV in-vitro.(11).

4. Biochemists could currently produce about 10 compounds with potentially antiviral properties, by adding methyl-, cyano- and other chemical groups to nucleoside bases. A number of other nucleoside derivatives which show considerable activity in-vitro are now under study for safety and tolerance(12);

. 3'-azido-2'-3'-dideoxy-5-ethyluridine (CS-85)
. 3'-azido-2'-3'-dideoxyguanosine
. 2'-3'-dideoxythymidine
. 2'-3'-dideoxythymidinene
. 2'-3'-dideoxycytidinene
. 2'-3'-dideoxyadenosine (DDA), and
. 2'-3'-dideoxyinosine (DDI)

(Several pharmaceuticals companies are awaiting the U.S. government's assessment of their application to manufacture DDA and DDI.)

B Didehydro compounds

Another two compounds:
2',3'-didehydro-2',3'-dideoxythymidine (DHT) and
2',3'-didehydro-2',3'-dideoxycytidine (DHC)

warrant further investigation of their use for the treatment of AIDS and related diseases. Current experimental findings indicate that DHT AND DHC efficiently inhibited the cytopathic effects and expression of HIV-specific antigens in MT-4 cells after infection with HIV. Both DHT and DHC also strongly blocked viral replication as determined by a quantitative bioassay system using a plaque-forming assay[13]. These antiviral effects were obtained at concentrations at which the drugs produced little or no toxicity and were comparable to those with AZT and 2'3'-dideoxy- nucleosides.

C Several other agents have now been evaluated for their activity against HIV in-vitro. Of these, few have shown sufficient activity to warrant further investigation in patients. Most of these have been inhibitors of reverse transcriptase, including:

1. Suramin (a hexasodium salt derivative of naphthalene-trisulphonic acid) is a polyaromatic, polysulphonic acid that has been used extensively in humans for the treatment of trypanosomiasis and onchocerciasis. In addition to inhibiting reverse transcriptase, suramin also inhibits in-vitro replication of HIV in both a neoplastic T cell line and a healthy antigen-specific T4 clone[14].

   Suramin produced no clinical or immunological efficacy in a study of 18 AIDS patients treated for 6 months. A high frequency of adrenal insufficiency (33% of patients) was seen with plasma concentrations greater than 100 ug/mL. Such levels are often reached when treating patients with parasitic diseases. Other adverse reactions observed were skin eruptions, fever, photosensitivity, proteinuria, elevated liver transaminases, pyuria and a burning sensation of the extremities.

2. HPA - 23 (antimoniotungstate - a cryptate mineral condensed polyanion of constitution ammonium 21 - tungsto- 9 - antimoniate) acts as a competitive inhibitor of murine oncornaviruses and is active in-vivo against a broad spectrum of RNA and DNA viruses[15]. In mice infected with slow viruses, HPA-23 has neurotropic effects and inhibits the reverse transcriptase of both HIV and Simian AIDS virus[16].

   In a summary published on clinical trials of antiviral therapy among AIDS patients, no clinical improvement was noted among patients on HPA-23, although HIV disappeared during therapy in some patients[16]. However viraemia reappeared after therapy was discontinued. Common adverse reations were thrombocytopenia, hepatic dysfunction, and fever.

3. Foscarnet (trisodium phosphonoformate - a pyrophosphate analogue) acts as a non-competitive in-vitro inhibitor for substrates and templates of reverse transcriptases from various animal retroviruses in doses ranging from 0.7 to 100 µM. These retroviruses include murine leukaemia viruses, simian sarcoma virus, baboon endogenous virus, bovine leukaemia virus, and visna virus[17]. Their

replication is inhibited in cell cultures by doses ranging from 100 to 500 µM.
Foscarnet has been used primarily as an inhibitor of herpes virus DNA polymerases with topical use for the treatment of recurrent herpes labialis and herpes genitalis, and systemically for the treatment of cytomegalovirus infection.

Tested on HIV replication in human (H9) cell line, this agent inhibited reverse transcriptase activity in doses ranging from 0.1 to 5.0 µM[18]. In-vitro infection was monitored by cytopathic effects, reverse transcriptase activity, indirect immunofluorescence, and virus-yield assays with dose-dependent inhibition of HIV-replication seen at doses ranging from 132 to 680 µM. This higher dose (680 µM) still inhibited replication when added as late as 48 to 96 hours after viral infection, and did not appear to significantly impair cell multiplication. Clinical studies suggest that doses of 132 to 680 µM are non-toxic. Foscarnet is currently in Phase-2 clinical trials as an anti-HIV agent:-

. a Swedish study reported that ARC patients treated with intravenous foscarnet for periods of 2 to 3 weeks experienced improvements in night sweats, bowel disturbances and "flu-like" symptoms. No significant changes were observed in immunological variables, but there was a reduction in the incidence of positive HIV cultures.

STAGE 3

. Transactivation: The DNA is then circularised, and some of it is integrated into the host chromosomes, where it remains in a quiescent (proviral) form until the infected cell is activated. At that point, proviral DNA is transcribed into viral DNA. This HIV genome includes the genes tat-III and trs-art, which code for transactiviting factors that regulate viral gene expression.

- the tat-III gene codes for a transactivator protein that increases the rate of synthesis of virus by regulating the transcription of viral RNA or the translation of mRNA into viral proteins or both.

- the product of the trs-art gene may act after transcription to relieve negative regulation of viral RNAs coding for capsid and envelope proteins.

STAGE 4

. Post-transcriptional processing and translation: the viral RNA, transcribed from proviral DNA, is processed before binding to ribosomes to initiate translation and synthesis of virus-specific proteins. Some of these proteins are cleaved to smaller forms and glycosylated.

A An inhibitor of such viral transcription is ribavirin.

. Ribavirin (1-β-ribofuranosyl-1,2,4-triazole-3 carboxamide), marketed as Virazole, is a guanosine analogue with broad-spectrum activity against many DNA and RNA viruses. Ribavirin a is nucleoside compound with ribose and triazole moieties[12]. Several modes of ribavirin

inhibition of viral replication are proposed but the compound is believed to be primarily a competitive inhibitor of guanosine in the 5' capping of viral messenger RNA[19].

Ribavirin is used in clinical trials in the US to delay or prevent development of AIDS in patients with generalised lymphadenopathy. Phase-1 studies have been conducted in both patients with AIDS and patients with AIDS-related complex:

. in one study, 7 of 9 patients initially positive for HIV became virus-free during treatment, but in 5 of the 7, HIV cultures became positive once therapy was discontinued.
. in another double-blind, placebo-controlled trial where 163 patients with persistent generalised lymphadenopathy, were given daily oral doses of 600 or 800 mg were compared with a placebo over a 6-month period:
  - 10 of 56 patients (18%) in the placebo group, developed AIDS during the period of observation,
  - 6 of 55 patients (11%) in the 600mg-group, developed AIDS during the study period, and
  - none of 52 patients in the 800mg-group developed AIDS in the specified period.

Few details of these studies have been published. Ribavirin therapy has been associated with anaemia due to haemolysis and inhibition of haemoglobin synthesis [20]. These adverse reactions may limit the drug's usefulness[21].

In addition to considering ribavirin as a single agent, experimental therapies for AIDS using a combination of Ribavirin and AZT have produced antagonistic effects in-vitro. Unlike many drug combinations which show synergistic interactions, ribavirin was, in six separate in-vitro experiments, shown to:

- antagonise the antiviral activity of AZT, and
- induce toxicity towards the cells being used[22].

Ribavirin inhibits the phosphorylation of AZT to its active triphosphate form, probably by increasing deoxythymidine triphosphate levels and resulting in a feedback inhibition of thymidine kinase.

Caution is now urged in future clinical trials of this combination or other drugs with similar metabolic pathways, although in-vitro interactions may not necessarily reflect conditions in-vivo. While studies of the pharmacokinetic interactions of the AZT-ribavirin combination in animals are planned, the drug is now the subject of a heated debate. The U.S. Food and Drug

Administration (FDA) has refused a request from the manufacturer to supply ribavirin on compassionate grounds to sufferers of generalised lymphadenopathy syndrome, on the grounds that there was insufficient evidence of its efficacy. Other medical and regulatory authorities share misgivings about the company's claims for the drug. The FDA is now investigating claims the company made about its efficacy against another virus, the respiratory syncytial virus.

B Hybridons, which oligonucleotides that have been synthesised as complementary sequences to certain regions of the HIV RNA or mRNA[41], may act as competitive inhibitors at the level of transcription or translation. This hybridisation competition has been called the "antisense RNA" approach. Whether such an approach will be applicable in-vivo is unclear.

STAGE 5

. Assembly and release: Viral glycoproteins are synthesised and glycosylated in the rough endoplasmic reticulum and transported through the Golgi apparatus to the plasma membrane. Then the genomic RNA and viral proteins are assembled, and virus particles are released by budding through the plasma membrane.

A. The inhibition of viral budding of the mature virus can be induced by the interferons which are natural proteins, produced during viral infections and antigenic challenge. Not only alpha-interferon but also beta- and gamma-interferons, as well as granulocyte-macrophage colony-stimulating factor, have some activity against HIV in-vitro.

. Alpha-interferon, a class of T cell-derived lymphokine which consists of 14 different polypetides, seems to have both antiviral activity and the ability to enhance cytotoxic monocyte/macrophage function[23]. The recombinant product has been used with some success in AIDS patients with Kaposi's sarcoma where various degrees of regression, if not complete remission was noted in several patients[24]. In a more recent report, patients with AIDS and Kaposi's sarcoma of various degrees of severity were treated with alpha-interferon, and a direct relationship was noted between the efficacy of the alpha-interferon and the baseline immunologic status of the patient (the greater the competence of the immune system, the better the chance of a partial or even complete remission)[25].

B. Immunomodulators

Patients with AIDS have a profound defect in multiple components of their immune system. Although this defect is manifested by heterogeneous immunologic abnormalities, the underlying deficiency is related to a selective abnormality of the T4 helper-inducer subset of T lymphocytes caused by infection of that subset with HIV[4]. Attempts to reconstitute or enhance the defective immune system in these patients involve using immunomodulators to enhance the patient's immune competence.

1. Gamma-interferon, also a T cell-derived glycoprotein, is a pure immunomodulator unlike alpha-interferon which has antiviral and antiproliferative effects in addition to immunomodulatory effects. Gamma-interferon has the ability to enhance the cytotoxic function of macrophages[26]. It

has been used in phase-1 clinical trials in patients with Kaposi's sarcoma. Side effects were substantial and it does not appear to be of clinical value as a single agent[27,28].

NB. It has been noted that in general, results of preliminary human trials were not encouraging: at dosage levels where immunologic enhancement is expected, patients had unacceptable toxicity with alpha- , beta- and gamma-interferon although it is observed that human alpha-and beta-interferon but not gamma suppress the in-vitro replication of LAV, HIV and ARV-2[29]. Because of inherent toxicity with alpha- , beta- , and gamma-interferons, researchers have focused attention on interleukin-2.

2. Interleukin-2, a T cell growth factor, is a T-cell-derived lymphokine with potent immunoenhancing properties in-vitro (ie it induces the expansion of activated T-cell populations, the differentiation of cytotoxic T cells, and the enhancement of B-cell activation). This glycoprotein, available as both a natural product and a recombinant product, is capable of markedly enhancing the in-vitro killer cells activities of lymphocytes from both controls and patients with AIDS[30]. From this in-vitro finding, phase-1 clinical studies were undertaken in which patients were administered continuous intravenous infusions of recombinant interleukin-2 in doses ranging from 250 units to 2.5 million units over 24 hours for 5 of 7 days. These studies were initially carried out for 4 weeks and were subsequently extended to a total of 8 weeks.

   Preliminary studies with the maximally tolerated dose (2 to 2.5 million units per 24 hours) resulted in:

   . an initial elevation of the total numbers of circulating T4 lymphocytes, followed by a return to baseline value despite continued infection,
   . a decrease in isolation of HIV from peripheral blood lymphocytes, and
   . an increase in spontaneous lymphocyte proliferation, together with minor tumor regressions.

C. Various other compounds have been used in clinical trials to enhance the immune system. Among these are:

1. Inosine pranobex - Isoprinosine - is a derivative of the nucleoside inosine, which was initially developed as an antiviral compound. When studied in-vitro, inosine pranobex has been shown to enhance T-cell activation.

In one clinical trial, it was capable of enhancing T-cell proliferative responses to the mitogen phytohaemagglutinin in certain patients with the AIDS related complex but had no effect on the immunologic function of patients with AIDS[31]. It is unclear whether inosine pranobex or any of the following compounds:

   . azimexon,
   . cimetidine,

. indomethacin,
. thymosin fraction 5, and
. transfer factor.

will be of clinical importance in the management of patients with AIDS or related illnesses.

2. Imuthiol (Diethyldithiocarbamate - DTC) is an immunostimulant which, according to French researchers, produces improvement in ARC patients and may delay the onset of AIDS in people with ARC, as observed in the following clinical studies:

. The study of imuthiol effects on 11 ARC patients showed an amelioration of symptoms and biological anomalies in 70% of patients; none of the patients has been cured and preliminary results noted increased white blood cell counts in recipients.

. In a double-blind placebo-controlled trial involving 90 ARC patients, inhibition clinical improvement, a rise in T4 cell levels and an inhibition of progression to AIDS, compared with the placebo group was noted after 4 months of treatment. No serious adverse effects were noted. After imuthiol treatment was ceased clinical benefit was lost and T4 cell values returned to pre-treatment levels.

Other clinical studies of imuthiol have been co-ordinated in the U.S.:

. a study of imuthiol involving 150 HIV antibody positive patients is in progress in six university-affiliated hospitals:

- results of a study of 20 pre-AIDS patients treated with imuthiol between October 1985 and July 1986, observed that patients who took 600 mg of the drug orally once a week felt better and the drug reduced swelling in lymph glands compared with placebo.

- a phase-3 trial is in progress with 130 patients taking part so far. This trial is expected to conclude by mid-1988(34).

(It is believed that imuthiol could be administered in combination with an antiviral drug(32)).

However, researchers in Belgium found no clinical improvement or T4 cell increase in 6 patients treated for 16 weeks with a combination of imuthiol and suramin. One patient devehowever developed adrenal insufficiency attributable to suramin,(33).

3. Ampligen is a mismatched double-stranded RNA polymer of the form $rI_n.r\ (C_{12}U)_n$, and is an inducer of all types of interferon. It is an intracellular activator of at least two enzymes induced by the interferons requiring double-stranded RNA for biological activity(35). Although $rI_n.C_n$ is highly toxic, introduction of uridine into its polycytidylic chain results in ampligen, a polymer with similar biological response modifier activities but without concomitant toxicity(36). In a

recent phase 1 clinical trial in terminal cancer patients, virtually no toxicity was associated with ampligen given intravenously[37].

Unlike the parent analogue, $rI_n.C_n$, ampligen did not induce antibodies to double-stranded nucleic acids. This dissociation of antibodies inducing potential and biological response modifier activity seems to be related to the shorter plasma half-life of ampligen (20 min)[37] compared with that of the parent analogue (4-6 hrs)[38].

Ampligen degradation in-vivo generates bioactive double stranded RNA fragments that apparently enter cells easily and cross the blood-brain barrier readily[39].

Ampligen has been shown to reduce the concentration of AZT required for virustasis of HIV in-vitro by at least 5-fold[34]. Moreover, at the higher concentrations of AZT tested, there seemed to be a synergistic relation between the two compounds since a complete protection was provided by combined suboptimal doses of each drug[40]. It was therefore predicted that ampligen would reduce the dose of AZT required for a therapeutic effect in-vivo, and hence the exposure to AZT-associated toxicity. Since the two drugs have entirely different modes of action, it is unlikely that they will exert toxicities other than those associated with each drug alone.

Indeed, no evidence of synergistic toxicity has been observed clinically, even when ampligen was combined with closely allied molecules such as the interferons[40].

Moreover, since ampligen has demonstrated immunomodulatory activities clinically [37] as well as antiviral properties (both possibly mediated through similar mechanisms such as the 2'-5' oligo A pathway), its use together with AZT may have pronounced and long-term beneficial effects on the course of AIDS beyond that which can be estimated in-vitro.

REFERENCES

1. NEJM (1985) 313: 1389-90
2. Science (1987) 237: 128-30
3. Biochim Biophys. Acta (1985) 812: 133-8
4. Science (1984) 224: 497-500
5. Lancet (1987) Jun 20: 1428
6. Proc. Natl. Acad. Sci. USA (1986) 83: 8333-37
7. J. Med. Chem. (1986) 29: 1561-69
8. NEJM (1987) 317 (4): 192-197
9. NEJM (1987) 317 (4): 185-191
10. Brochem. Pharmacol. (1986) 35: 2065-68
11. New Scientist (1987) 23/7: 22
12. J. Med. Chem. (1972) 15: 1150-4
13. Antimicrob. Agents and Chemother. (1987) 31: 907-10
14. Science (1984) 226: 172-4
15. J. Gen. Virol. (1976) 31: 59-64

16. Report of AIDS antiviral workshop (1985)
17. Pharmac. Ther. (1983) 19: 387-415
18. Lancet (1985) i: 1480-2
19. Biochem. Biophys. Res. Commun. (1979) 89: 830-6
20. Antimicrob. Agents and Chemother. (1987) 30: 201-205
21. Lancet (1986) ii: 45-46
22. Science (1987) 235: 1376-9
23. Lancet (1985) i: 602-604
24. NEJM (1983) 308: 1071-6
25. Am. J. Med. (1985) 78: 737-41
26. Ann. Intern. Med. (1985) 103: 704-709
27. Clin. Res. (1985) 33: 408A
28. NEJM (1984) 311: 1099-103
29. J. Interferon. Res. (1986) 6: 143-152
30. J. Clin. Invest. (1983) 72: 398-403
31. Ann. Inter. Med. (1984) 101: 206-7
32. CDC AIDS Weekly (1987) 15 June: 6
33. Scrip (1987) 1215: 22
34. Lancet (1987) i: 891-82
35. Prog. Clin. Path. (1983) 9: 101-19
36. J. Molec. Biol. (1972) 70: 567-87
37. J. Biol. Resp. Modifiers (1985) 4: 669-75
38. J. Biol. Resp. Modifiers (1985) 4: 495-502
39. Biochem. Biophys. Res. Commun. (1986) 138: 40-6
40. Am. Soc. Clin. Oncol. (in press)
41. Proc. Natl. Acad. Sci. USA (1986) 83: 4143-46

GUIDELINES FOR COUNSELLING AND ANTIBODY TESTING TO PREVENT HIV INFECTION AND AIDS - PUBLIC HEALTH SERVICE (U.S.A.)

(Extracted from MMWR Vol.36/No.31, 14 August 1987)

Human immunodeficiency virus (HIV), the causative agent of acquired immunodeficiency syndrome (AIDS) and related clinical manifestations, has been shown to be spread:

- by sexual contact,
- by parenteral exposure to blood (most often through intravenous [IV] drug abuse) and, rarely, by other exposures to blood; and
- from an infected woman to her fetus or infant.

Persons exposed to HIV usually develop detectable levels of antibody against the virus within 6-12 weeks of infection. The presence of antibody indicates current infection, though many infected persons may have minimal or no clinical evidence of disease for years. Counselling and testing persons who are infected or at risk for acquiring HIV infection is an important component of prevention strategy(1). Most of the estimated 1.0 to 1.5 million infected persons in the United States are unaware that they are infected with HIV. The primary public health purposes of counselling and testing are to help uninfected individuals initiate and sustain behavioral changes that reduce their risk of becoming infected and to assist infected individuals in avoiding infecting others.

Along with the potential personal, medical, and public health benefits of testing for HIV antibody, public health agencies must be concerned about actions that will discourage the use of counselling and testing facilities, most notably the unauthorised disclosure of personal information and the possibility of inappropriate discrimination.

Priorities for public health counselling and testing should be based upon providing ready access to persons who are most likely to be infected or who practice high-risk behaviors, thereby helping to reduce further spread of infection. There are other considerations for determining testing priorities, including the likely effectiveness of preventing the spread of infection among persons who would not otherwise realise that they are at risk. Knowledge of the prevalence of HIV infection in different populations is useful in determining the most efficient and effective locations for providing such services. For example, programs that offer counselling and testing to homosexual men, IV-drug abusers, persons with haemophilia, sexual and/or needle-sharing partners of these persons, and patients of sexually transmitted disease clinics may be most effective since persons in these groups are at high risk for infection. After counselling and testing are effectively implemented in settings of high and moderate prevalence, consideration should be given to establishing programs in settings of lower prevalence.

INTERPRETATION OF HIV-ANTIBODY TEST RESULTS

A test for HIV antibody is considered positive when a sequence of tests, starting with a repeatedly reactive enzyme immunosorbent assay (ELISA) and including an additional, more specific assay, such as a Western blot, are consistently reactive.

The sensitivity of the currently licensed ELISA tests is 99% or greater when performed under optimal laboratory conditions. Given this performance, the probability of a false-negative test result is remote, except during the first weeks after infection, before antibody is detectable.

The specificity of the currently licensed ELISA tests is approximately 99% when repeatedly reactive tests are considered. Repeat testing of specimens initially reactive by ELISA is required to reduce the likelihood of false-positive tests results due to laboratory error. To further increase the specificity of the testing process, laboratories must use a supplement test - most often the Western blot test-to validate repeatedly reactive ELISA results. The sensitivity of the licensed Western blot test is comparable to that of the ELISA, and it is highly specific when strict criteria are used for interpretation. Under ideal circumstances, the probability that a testing sequence will be falsely positive in a population with a low rate of infection ranges from less than 1 in 100,000 (Minnesota Department of Health, unpublished data) to an estimated 5 in 100,000[2,3]. Laboratories using different Western blot reagents or other tests or using less stringent interpretive criteria may experience higher rates of false-positive results.

Laboratories should carefully guard against human errors, which are likely to be the most common source of false-positive test results. All laboratories should anticipate the need for assuring quality performance of tests for HIV antibody by:

. training personnel,
. establishing quality controls, and
. participating in performance evaluation systems.

Health department laboratories should facilitate the quality assurance of the performance of laboratories in their jurisdiction.

GUIDELINES FOR COUNSELLING AND TESTING FOR HIV ANTIBODY

These guidelines are based on public health considerations for HIV testing including the principles of counselling before and after testing, confidentiality of personal information, and the understanding that a person may decline to be tested without being denied health care or other services, except where testing is required by law(4). Counselling before testing may not be practical when screening for HIV antibody is required. This is true for donors of blood, organs, and tissue; prisoners; and immigrants for whom testing is a Federal requirement; as well as for persons admitted to state correctional institutions in states that require testing. When there is no counselling before testing, persons should be informed that testing for HIV antibody will be performed, that individual results will be kept confidential to the extent permitted by law, and the appropriate counselling will be offered. Individual counselling of those who are either HIV-antibody positive or at continuing risk for HIV infection is critical for reducing further transmission and for ensuring timely medical care.

Specific recommendations follow:

1. Persons who may have sexually transmitted disease. All persons seeking treatment for a sexually transmitted disease, in all health-care settings including the offices of private physicians, should be routinely ("Routine counselling and testing" is defined as a policy to provide these services to all clients after informing them that testing will be done. Except where testing is required by law, individuals have the right to decline to be tested without being denied health care or other services.) counselled and tested for HIV antibody.

2. IV-drug abusers. All persons seeking treatment for IV-drug abuse or having a history of IV-drug abuse should be routinely counselled and tested for HIV antibody. Medical professionals in all health-care settings, including prison clinics, should seek a history of IV-drug abuse from patients and should be aware of its implications for HIV infection. In addition, state and local health policy makers should address the following issues:

   . Treatment programs for IV-drug abusers should be sufficiently available to allow persons seeking assistance to enter promptly and be encouraged to alter the behavior that places them and others at risk for HIV infection.

. Outreach programs for IV-drug abusers should be undertaken to increase their knowledge of AIDS and of ways to prevent HIV infection, to encourage them to obtain counselling and testing for HIV antibody, and to persuade them to be treated for substance abuse.

3. Persons who consider themselves at risk. All persons who consider themselves at risk for HIV infection should be counselled and offered testing for HIV antibody.

4. Woman of childbearing age. All women of childbearing age with identifiable risks for HIV infection should be routinely counselled and tested for HIV antibody, regardless of the health-care setting. Each encounter between a health-care provider and a woman at risk and/or her sexual partners is an opportunity to reach them with information and education about AIDS and prevention of HIV infection. Women are at risk for HIV infection if they:
. have used IV drugs.
. have engaged in prostitution.
. have had sexual partners who are infected or are at risk for infection because they are bisexual or are IV-drug abusers or haemophiliacs.
. are living in communities or were born in countries where there is a known or suspected high prevalence of infection among women.
. received a transfusion before blood was screened for HIV antibody but after HIV infection occurred in the United States (e.g., between 1978 and 1985).

Educating and testing these women before they become pregnant allows them to avoid pregnancy and subsequent intrauterine perinatal infection of their infants (30%-50% of the infants born to HIV-infected women will also be infected).

All pregnant women at risk for HIV infection should be routinely counselled and tested for HIV antibody. Identifying pregnant women with HIV infection as early in pregnancy as possible is important:
. for ensuring appropriate medical care for these women;
. for planning medical care for their infants; and for
. providing counselling on family planning, future pregnancies, and the risk of sexual transmission of HIV to others.

All women who seek family planning services and who are at risk for HIV infection should be routinely counselled about AIDS and HIV infection and tested for HIV antibody. Decisions about the need for counselling and testing programs in a community should be based on the best available estimates of the prevalence of HIV infection and the demographic variables of infection.

5. Persons planning marriage. All persons considering marriage should be given information about AIDS, HIV infection, and the availability of counselling and testing for HIV antibody. Decisions about instituting routine or mandatory premarital testing for HIV antibody should take into account the prevalence of HIV infection in the area

and/or population group as well as other factors and should be based upon the likely cost-effectiveness of such testing in preventing further spread of infection. Premarital testing in an area with a prevalence of HIV infection as low as 0.1% may be justified if reaching an infected person through testing can prevent subsequent transmission to the spouse or prevent pregnancy in a woman who is infected.

6. Persons undergoing medical evaluation or treatment. Testing for HIV antibody is useful diagnostic tool for evaluating patients with selected clinical signs and symptoms such as generalised lymphadenopathy; unexplained dementia; chronic, unexplained fever or diarrhoea; unexplained weight loss; or diseases such as tuberculosis as well as sexually transmitted diseases, generalised herpes, and chronic candidiasis.
Since persons infected with both HIV and the tubercle bacillus are at high risk for severe clinical tuberculosis, all patients with tuberculosis should be routinely counselled and tested for HIV antibody(5). Guidelines for managing patients with both HIV and tuberculous infection have been published(6).

The risk of HIV infection from transfusions of blood or blood components from 1978-1985 was greatest for persons receiving large numbers of units of blood collected from areas with high incidences of AIDS. Persons who have this increased risk should be counselled about the potential risk of HIV infection and should be offered antibody testing(7).

7. Persons admitted to hospitals. Hospitals, in conjunction with state and local health departments, should periodically determine the prevalence of HIV infections in the age groups at highest risk for infection. Consideration should be given to routine testing in those age groups deemed to have a high prevalence of HIV infection.

8. Persons in correctional systems. Correctional systems should study the best means of implementing programs for counselling inmates about HIV infection and for testing them for such infection at admission and discharge from the system. In particular, they should examine the usefulness of these programs in preventing further transmission of HIV infection and the impact of the testing programs on both the inmates and the correctional system. Federal prisons have been instructed to test all prisoners when they enter and leave the prison system.

9. Prostitutes. Male and female prostitutes should be counselled and tested and made aware of the risks of HIV infection to themselves and others. Particularly prostitutes who are HIV-antibody positive should be instructed to discontinue the practice of prostitution. Local or state jurisdictions should adopt procedures to assure that these instructions are followed.

PARTNER NOTIFICATION/CONTACT TRACING

Sexual partners and those who share needles with HIV-infected

persons are at risk for HIV infection and should be routinely counselled and tested for HIV antibody. Persons who are HIV-antibody positive should be instructed in how to notify their patners and to refer them for counselling and testing. If they are unwilling to notify their partners or if it cannot be assured that their partners will seek counselling, physicians or health department personnel should use confidential procedures to assure that the partners are notified.

CONFIDENTIALITY AND ANTIDISCRIMINATION CONSIDERATIONS

The ability of health departments, hospitals, and other health-care providers and institutions to assure confidentiality of patient information and the public's confidence in that ability are crucial to efforts to increase the number of persons being counselled and tested for HIV infection. In addition, to assure broad participation in the counselling and testing programs, it is of equal or greater importance that public perceive that persons found to be positive will not be subject to inappropriate discrimination.

Every reasonable effort should be made to improve confidentiality of test results. The confidentiality of related records can be improved by a careful review of actual record-keeping practices and by assessing the degree to which these records can be protected under applicable state laws. State laws should be examined and strengthened when found necessary. Because of the wide scope of "need-to-know" situations, because of the possibility of inappropriate disclosures, and because of established authorisation procedures for releasing records, it is recognised that there is no perfect solution to confidentiality problems in all situations. Whether disclosures of HIV-testing information are deliberate, inadvertent, or simply unavoidable, public health policy needs to carefully consider ways to reduce the harmful impact of such disclosures.

Public health prevention policy to reduce the transmission of HIV infection can be widened by an expanded program of counselling and testing for HIV antibody, but the extent to which these programs are successful depends on the level of participation. Persons are more likely to participate in counselling and testing programs if they believe that they will not experience negative consequences in areas such as employment, school admission, housing, and medical services should they test positive. There is no known medical reason to avoid an infected person in these and ordinary social situations since the cumulative evidence is strong that HIV infection is not spread through casual contact. It is essential to the success of counselling and testing programs that persons who are tested for HIV are not subjected to inappropriate discrimination.

REFERENCES

1. MMWR (1986) 35 : 152-5
2. Ann Intern Med (1987) 106 : 671-6
3. NEJM (1987) 317 : 238-41
4. JAMA (1986) 256 : 1768-74
5. MMWR (1987) 36 : 254-5
6. MMWR (1986) 35 : 448-52
7. MMWR (1987) 36 : 137-40

RUBELLA VACCINATION DURING PREGNANCY - USA - 1971 - 1986.
(based on MMWR Vol 36, No.28, 24 July 1987)

From January 1971 through December 1986, the Centers for Disease Control (CDC) received reports of 1176 pregnant women who were given live attenuated rubella vaccine within either 3 months before or 3 months after their presumed dates of conception. These women were followed prospectively to determine the risk of fetal abnormalities following exposure to three types of licensed vaccines.

CENDEHILL AND HPV-77 VACCINES

Before 1979, data were collected on 538 women vaccinated during pregnancy with either Cendehill or HPV-77 rubella vaccines[1]. None of the 290 infants born to these women had defects indicative of congenital rubella syndrome (CRS)[2]; however, eight infants had serologic evidence of intra-uterine infection[1,3]. Three other women who received unknown strains of rubella vaccine delivered healthy infants who appeared normal.

RA 27/3 VACCINE

Since licensure of the RA 27/3 rubella vaccine in January 1979, CDC has received reports of 635 who were given this vaccine during pregnancy (Table 1):

- 224 of these women had negative serologic testing for rubella within 12 months of vaccination and were, therefore, susceptible at the time of vaccination.
  - outcomes of pregnancy are known for 211 (94%) of these susceptible women. Of the 211 women, 170 (81%) delivered 172 living infants.
- an additional 30 immune women and 319 women of unknown immune status delivered 350 living infants.

All these 522 infants were free of defects indicative of CRS.

Outcomes of the 116 pregnancies that did not result in known live births are presented in Table 1.

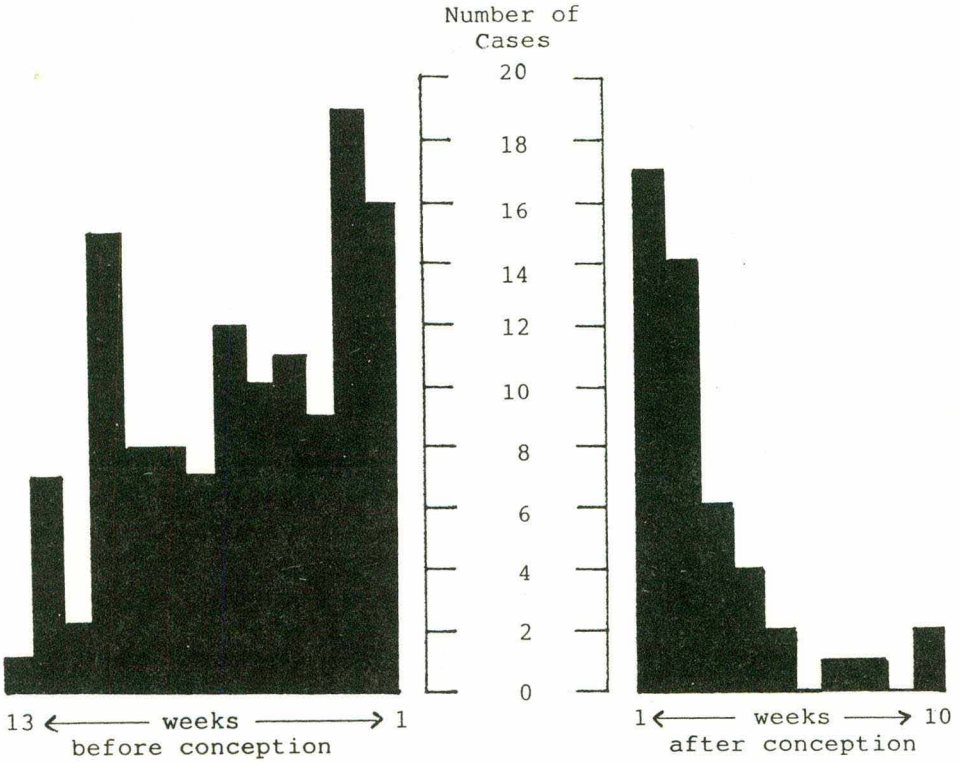
TABLE 1: Pregnancy outcomes for 635 recipients of RA 27/3 vaccine United States, January 1979-December 1986.

Prevaccination Immunity Status	Total Women	Live Births	Spontaneous Abortions and Stillbirths	Induced Abortions	Outcome Unknown
Susceptible	224	172*	11	30	13
Immune	32	30	1	0	1
Unknown	379	320+	8	24	28
Total	635	522	20	54	42

*Includes two twin births.
+Includes one twin birth.

The dates of vaccination and estimated dates of confinement were known for all of the 170 susceptible women who had full-term pregnancies (figure 1).

FIGURE 1. Interval, in weeks, between receipt of rubella RA 27/3 vaccine and estimated date of conception among 170 susceptible women with live births- United States, January 1979-December 1986.



Fifty-five women (32%) were vaccinated within 1 week before to 4 weeks after conception, the period of presumed highest risk for viraemia and fetal malformations.

Serologic evaluations were performed on 136(79%) of the 172 infants whose mothers were susceptible. Three (2%) of the 136 infants had normal examinations but measurable titres to rubella-specific IgM in cord blood, initially suggesting a sub-clinical infection. Prior to July 1985, the CDC laboratory performed haemagglutination inhibition (HI) tests for both rubella-specific IgM antibody and total rubella-antibody titres. Such testing revealed that:

. one infant who appeared normal had a rubella-specific IgM antibody titre of 8 in cord blood and a corresponding total rubella antibody titre of 128;
. the mother's total rubella antibody titre was also 128.

Simultaneous testing of cord blood and testing of a follow-up specimen taken when the infant was 2 months old showed a decrease in the titre of maternally derived antibody from 64 to 16 over the 2-months period, suggesting that subclinical infection may not have occurred. The infant had no evidence of defects indicative of CRS either at birth or at the 18-month and 29-month follow-up examinations. Sera could not be obtained for further follow-up testing to measure HI antibodies.

Since July 1985, the CDC laboratory has tested for rubella-specific IgG antibody using an indirect enzyme-linked immunosorbent assay (ELISA). Rubella-specific IgM antibodies were detected by ELISA using the same antigen-coated plates,

but with an enzyme-conjugated anti-human IgM serum. For IgM testing, sera were absorbed with staphylococcal protein A to remove IgG and to eliminate interference by rheumatoid factor. An IgM index was calculated for each serum using a known low-positive IgM serum as a reference standard:

. An IgM index 1.0 was considered positive, with increasing values indicating higher antibody levels. Using these tests, two additional infants who appeared normal, had cord sera that were positive for rubella IgM.

Serologic studies were also obtained on 156 of the 320 infants (Table 1) born to mothers whose immune status was unknown at the time of vaccination[4]. Subclinical infection was documented in two infants:

. One infant had a rubella-specific HI IgM antibody titre of 16 in cord blood. Both mother and infant had titres of 32 by HI at the time of birth, the infant still had a titre of 32 at 4 months of age. This infant had no evidence of defects indicative of CRS at birth or at the 10-month and 17-month examinations. A serum specimen was not obtained at subsequent follow-up visits.

. The second infant had a persistent HI titre of 8 at 3 months of age, suggesting that there had been subclinical infection. This infant was diagnosed as normal at the 3 months follow-up examination.

While none of the 172 infants born to susceptible women had defects indicative of CRS, two infants did have asymptomatic glandular hypospadias. However, both had negative rubella-specific IgM titres (<4) in cord blood at birth. Serum taken at the 6-month follow-up examination was available for one of the infants; he had a rubella-specific HI antibody titre of <8 (i.e., a negative titre).

Thirty susceptible women elected to have induced abortions (Table 1). Products of conception were available for viral isolation studies from 19 of these women, from two women who spontaneously aborted, and from 13 women whose case histories have been reported in the literature[5-7]. Rubella virus has been isolated from the products of conception of one (3%) of these 34 susceptible women.

MMWR Editorial Note:

Since 1971, CDC has maintained a register to monitor and quantitate the risk to the fetus of exposure to live attenuated rubella vaccine virus. Data are obtained through reports from physicians and state and local health departments as well as directly from women vaccinated within either 3 months before or 3 months after conception. Follow-up study is conducted to determine the outcome of each pregnancy. In 1979, when RA 27/3 rubella vaccine replaced the other rubella vaccines, there was concern that it might have greater fetotropic and tetarogenic potential than earlier vaccines. Data collected so far show that the RA 27/3 rubella vaccine, like the other vaccines, has not caused defects compatible with CRS.

Fifty-five (32%) of the 170 susceptible mothers were vaccinated with RA 27/3 vaccine during the highest risk period for viraemia and fetal defects (1 week before to 4 weeks after conception)[8,9]. Neither the infants born to these

high-risk women nor those born to any of the other women had CRS. Therefore, the observed risk of CRS following rubella vaccination continues to be nil (Table 2).

TABLE 2: Maximum theoretical risks of congenital rubella syndrome (CRS) following rubella vaccination, by vaccine strain - United States, 1971-1986*

Vaccine Strain	Susceptible Vaccinees	Normal Live Births	Observed	Risk of CRS Theoretical
RA 27/3	170	172**	0	0%-2.1%
Cendehill or HPV-77	94	94	0	0%-3.8%
Unknown	1	1	0	-
Total	265	267	0	0%-1.4%

*Through December 31, 1986. No women entered after 1980 in CDC's register of those receiving rubella within 3 months before or after conception were vaccinated with Cendehill or HPV-77 vaccine.

**Includes two twin births.

However, based on the 95% confidence limits of the binomial distribution, the theoretical maximum risk for the occurrence of CRS in this group of 172 children could be high as 2.1%. If the 95 infants exposed to other rubella vaccines are included, the maximum theoretical risk is 1.4% (Table 2). This overall maximum risk remains far less than the 20% or greater risk of congenital rubella syndrome (CRS) associated with maternal infection with wild rubella virus during the first trimester of pregnancy[3] and is no greater than the 2%-3% rate of major birth defects in the absence of exposure to rubella vaccine[10].

These favourable data are consistent with the experiences in the Federal Republic of Germany and the United Kingdom[11,12]. The vaccine has not been associated with the occurrence of CRS among infants born to susceptible mothers who had been vaccinated in either country:

- in Germany, 98 susceptible women vaccinated with either the Cendehill or RA 27/3 strain of vaccine gave birth to infants without CRS, and
- in the United Kingdom, none of 21 infants born to susceptible mothers (not all of whom were prospectively followed) had defects compatible with CRS.

The occurrence of any congenital defect following maternal vaccination deserves careful analysis and follow-up. In the U.S series:

- two infants born to susceptible mothers had asymptomatic glandular hypospadias. While hypospadias has been noted in CRS cases[13,14], there are no data to suggest that glandular hypospadias should be considered a CRS-associated defect. In any case, neither of the two infants in question had serologic evidence of rubella virus infection.

. eight other infants born to mothers of unknown immune status and two born to mothers known to be immune at the time of vaccination had some type of defect[15].

However, none of the defects were compatible with CRS, and serologic testing, when done, did not confirm rubella virus infection.

While no CRS-like defects have been noted, it is clear that rubella vaccine viruses, including the RA 27/3 strain, can cross the placenta and infect the fetus:

. approximately 1%-2% of infants born to susceptible vaccinees had serologic evidence of subclinical infection, regardless of vaccine strain[3];
. although the rubella virus isolation rate from the products of conception of women who have received the RA 27/3 vaccine is only 3% (1/35), the rate of virus isolation from the products of conception of those receiving Cendehill and HPV-77 vaccines is 20% (17/85)[3].

These data indicate that the risk of placental or fetal infection from RA 27/3 vaccine is low.

Recognising that no amount of data collection can absolutely rule out a theoretical risk to the fetus, however small, the Immunisation Practices Advisory Committee (ACIP) continues to state that:

. pregnancy remains a contraindication to rubella vaccination because of the theoretical, albeit small, risk of CRS;
. reasonable precautions should be taken, to preclude vaccination of pregnant women, including asking women if they are pregnant, excluding those who say they are, and explaining the theoretical risks to the others; and
. because of the risk of CRS is so small as to be negligible, rubella vaccination of a pregnant woman should not ordinarily be a reason to consider interruption of pregnancy, even if vaccination does occur within 3 months of conception[16].

The Centers for Disease Control encourages reporting of cases to its register of women receiving rubella vaccine within 3 months before or after conception. Only cases involving women known to have been susceptible at the time of vaccination, by virtue of negative serologic testing within the preceding year, should be reported to the Division of Immunisation, Center for Prevention Services. Although laboratory services for culture of placental and fetal tissue are no longer routinely available, serologic testing of women who have been enrolled in the registry and of their infants continue to be available at CDC.

REFERENCES:

1. MMWR (1982) 31 : 477-81
2. MMWR (1986) 35 : 275-6, 281-4, 315
3. JAMA (1981) 246 : 1413-7

4. Rev Infect Dis (1985), 7 (suppl 1) : S95-102
5. Lancet (1981) 1 : 392
6. Am J Dis Child (1969) 118 : 262-3
7. J Pediatr (1980) 97 : 467-70
8. Lancet (1981) 2 : 1284
9. Lancet (1981) 1 : 1078-80
10. U.S Dept Health and Hum. Serv. PHS report (1985)
11. BMJ (1986) 292 : 727
12. Rev Infect Dis (1985) 7 (suppl 1) : S 103-7
13. Am J Dis Child (1969) 118 : 30-1
14. Pediatr Ann (1977) 6 : 762-72
15. MMWR (1983) 32 : 429-32, 437
16. MMWR (1984) 33 : 301-10, 315

AUSTRALIA - COMMUNICABLE DISEASES INTELLIGENCE

REPORTING PERIOD- 24-8-87 to 6-9-87 BULLETIN NUMBER 87/18
VIRAL IDENTIFICATIONS FROM CONTRIBUTING LABORATORIES

VIRUS OR VIRAL ANTIGEN	ICPMR (NSW)/ WVH (ACT)	RAHC (NSW)	PHH/ POW (NSW)	FAIR-FIELD (VIC)	RCH (VIC)	IMVS (SA)	STATE LAB (QLD)	STATE LAB (WA)	Total
0100 ADENOVIRUS NOT TYPED	2	1	3	5	9		8	5	33
0101 ADENOVIRUS TYPE 1				2					2
0102 ADENOVIRUS TYPE 2	1			2				1	4
0103 ADENOVIRUS TYPE 3				1					1
0105 ADENOVIRUS TYPE 5				1					1
0108 ADENOVIRUS TYPE 8				1					1
0199 ADENOVIRUS TYPING PENDING	1		1		4				6
0201 INFLUENZA A VIRUS		1		1		5		3	10
0202 INFLUENZA A VIRUS SUBTYPE H3N2				1	11				12
0203 INFLUENZA B VIRUS	5			11	2	2	4		24
0206 INFLUENZA A VIRUS SUBTYPE H1N1				1					1
0299 INFLUENZA VIRUS					3				3
0301 PARAINFLUENZA VIRUS TYPE 1					1	7		1	9
0302 PARAINFLUENZA VIRUS TYPE 2	1						1	1	3
0303 PARAINFLUENZA VIRUS TYPE 3	2	2	1		9	8	3	5	30
0399 PARAINFLUENZA VIRUS TYPING PENDING					3				3
0400 RESPIRATORY SYNCYTIAL VIRUS (RS)	14	24	3	31	28	30	23	23	176
0500 RHINOVIRUS (ALL TYPES)	6	1	1	1	6	2	4		21
0600 MYCOPLASMA PNEUMONIAE	9	2	2	12	2	5	21	4	57
0700 ORNITHOSIS-PSITTACOSIS	1			1				1	3
0816 COXSACKIEVIRUS A16								1	1
0902 COXSACKIEVIRUS B2				2		2			4
0903 COXSACKIEVIRUS B3	1	1						1	3
0905 COXSACKIEVIRUS B5				1					1
1005 ECHOVIRUS TYPE 5				1					1
1011 ECHOVIRUS TYPE 11				1		1			2
1014 ECHOVIRUS TYPE 14								1	1
1015 ECHOVIRUS TYPE 15								1	1
1018 ECHOVIRUS TYPE 18								1	1
1022 ECHOVIRUS TYPE 22				1					1
1027 ECHOVIRUS TYPE 27				1					1
1100 POLIOVIRUS NOT TYPED			3						3
1101 POLIOVIRUS TYPE 1	3	3							6
1102 POLIOVIRUS TYPE 2	1			1				1	3
1103 POLIOVIRUS TYPE 3						1			1
1200 MUMPS VIRUS	1			1				2	4
1300 HERPES VIRUS GROUP-NOT TYPED	30			1				2	33
1301 HERPES SIMPLEX VIRUS NOT-TYPED		1						2	3
1302 EPSTEIN-BARR VIRUS (EB VIRUS)	2		4	5		3	8	3	25
1303 VARICELLA-ZOSTER VIRUS	3		2	2		1	1	2	11
1306 HERPES SIMPLEX TYPE 1	28			36	1	16	51	23	155
1307 HERPES SIMPLEX TYPE 2	67			56		17	70	44	254
1399 HERPES VIRUS TYPING PENDING					3				3
1401 COXIELLA BURNETI	4			5		2	10	1	22
1502 PICORNA VIRUS-NOT TYPED	8		4						12
1521 MEASLES VIRUS				3					3
1522 RUBELLA VIRUS			1	1				1	3
1532 HEPATITIS B ANTIGEN	15	1	6	40		13	4	17	96
1535 HEPATITIS A ANTIBODY	3			1	2	10			16
1541 CHLAMYDIA A - C TRACHOMATIS	19	2	1	2		40	29	29	122
1556 CMV - CYTOMEGALOVIRUS	5	2	8	24	5	5	9	15	73
1564 ROTAVIRUS	20	5	20	14	21	16	31	9	136
1599 ENTEROVIRUS TYPING PENDING			10		7				17
9992 ROSS RIVER VIRUS				1			6		7
9994 SMALL VIRUS (LIKE) PARTICLE		1							1
9998 ARBO. GROUP B.				1			1		2
Total	252	47	70	272	117	186	284	200	1,428

AUSTRALIA - COMMUNICABLE DISEASES INTELLIGENCE

PERIOD : 24-8-87 to 6-9-87 BULLETIN NO 87/18

Viral Identifications by Clinical Information Table 1.
Code 00,99 -No ill or data; 01,02,11,12 -Respiratory; E3 -Encephalitis; M3 -Meningitis; 04 -Paralysis; 05,13 -CNS other unspec.; 07,49 -GI; 17,47 -Hepatic; 19 -CVS; 89 -Urinary; 06 -Skin/mucous.

VIRUS OR VIRAL ANTIGEN	No-ill or data	Respir atory	Enceph alitis	Mening -itis	Para- lysis	CNS other unspec	GI	Hepa -tic	CVS	Urin -ary	Skin/ mucs memb
0101 ADENOVIRUS TYPE 1.....		1									1
0102 ADENOVIRUS TYPE 2.....		2					1				2
0103 ADENOVIRUS TYPE 3.....	1										
0201 INFLUENZA A VIRUS.....		8				1	1	1			
0202 INFLUENZA A VIRUS SUBTYPE H3N2		11									
0203 INFLUENZA B VIRUS.....	4	20		1							
0206 INFLUENZA A VIRUS SUBTYPE H1N1		1		1							
0301 PARAINFLUENZA VIRUS TYPE 1....		9									
0302 PARAINFLUENZA VIRUS TYPE 2....		3									
0303 PARAINFLUENZA VIRUS TYPE 3....		29									
0400 RESPIRATORY SYNCYTIAL VIRUS (RS).....	2	170	1	1							1
0600 MYCOPLASMA PNEUMONIAE.....	9	46									1
0700 ORNITHOSIS-PSITTACOSIS.....		2									
0816 COXSACKIEVIRUS A16.....		1									
0902 COXSACKIEVIRUS B2.....		2		2							
0903 COXSACKIEVIRUS B3.....		1									
0905 COXSACKIEVIRUS B5.....				1							
1005 ECHOVIRUS TYPE 5.....						1					
1011 ECHOVIRUS TYPE 11.....		1		1							
1022 ECHOVIRUS TYPE 22.....		1									
1027 ECHOVIRUS TYPE 27.....							1				
1101 POLIOVIRUS TYPE 1.....	1	2	2				1				
1102 POLIOVIRUS TYPE 2.....		1					2				
1200 MUMPS VIRUS.....	1					1				1	
1301 HERPES SIMPLEX VIRUS NOT-TYPED				1							2
1302 EPSTEIN-BARR VIRUS (EB VIRUS).	3	4				1	1	2			1
1303 VARICELLA-ZOSTER VIRUS.....	2					1					6
1306 HERPES SIMPLEX TYPE 1.....	2	6								5	84
1307 HERPES SIMPLEX TYPE 2.....	7										82
1401 COXIELLA BURNETI.....	6	3						2			
1521 MEASLES VIRUS.....	1	2									1
1522 RUBELLA VIRUS.....											2
1532 HEPATITIS B ANTIGEN.....	33							56		1	
1535 HEPATITIS A ANTIBODY.....	3							5			
1541 CHLAMYDIA A - C.TRACHOMATIS...	5	2									
1556 CMV - CYTOMEGALOVIRUS.....	5	21					1	4		4	2
1564 ROTAVIRUS.....	1						133				
9992 ROSS RIVER VIRUS.....	2										1
9994 SMALL VIRUS (LIKE) PARTICLE...							1				
9998 ARBO. GROUP B.											1
Total.....	88	349	3	8		5	142	70		11	187

AUSTRALIA - COMMUNICABLE DISEASES INTELLIGENCE

PERIOD : 24-8-87 to 6-9-87 BULLETIN NO 87/18
Viral Identifications by Clinical Information Table 2.
Code 10 -Eye; 59 -Genital; 39 -Endo/sal gland;
38 -RES; 29 -Muscle/joint; 69 -Congenital; P8 -PUO;
G8 -Fever/malaise; 09 -Other; A1 -SIDS ...

VIRUS OR VIRAL ANTIGEN	Eye	Gen-ital	Endo/sal gland	RES	Muscle/joint	Con-genit-al	PUO	Fever/mal-aise	Other	SIDS
0105 ADENOVIRUS TYPE 5.....			1					1		
0108 ADENOVIRUS TYPE 8.....	1									
0201 INFLUENZA A VIRUS.....								1		
0202 INFLUENZA A VIRUS SUBTYPE H3N2										1
0303 PARAINFLUENZA VIRUS TYPE 3....	1						1			
0400 RESPIRATORY SYNCYTIAL VIRUS (RS).....							2	1		
0600 MYCOPLASMA PNEUMONIAE.....								12	1	
0700 ORNITHOSIS-PSITTACOSIS.....	1						1	1		
0903 COXSACKIEVIRUS B3.....						1		1		
1005 ECHOVIRUS TYPE 5.....								1		
1014 ECHOVIRUS TYPE 14.....										1
1015 ECHOVIRUS TYPE 15.....									1	
1018 ECHOVIRUS TYPE 18.....									1	
1027 ECHOVIRUS TYPE 27.....								1		
1103 POLIOVIRUS TYPE 3.....										1
1200 MUMPS VIRUS.....								1	1	
1302 EPSTEIN-BARR VIRUS (EB VIRUS).			8	1				6	5	
1303 VARICELLA-ZOSTER VIRUS.....									3	
1306 HERPES SIMPLEX TYPE 1.....	2	56						4	1	
1307 HERPES SIMPLEX TYPE 2.....		166								
1401 COXIELLA BURNETI.....					2		4	11		
1522 RUBELLA VIRUS.....								1		
1532 HEPATITIS B ANTIGEN.....									6	
1535 HEPATITIS A ANTIBODY.....									8	
1541 CHLAMYDIA A - C.TRACHOMATIS...		114							1	
1556 CMV - CYTOMEGALOVIRUS.....						4	3	8	27	
1564 ROTAVIRUS.....										2
9992 ROSS RIVER VIRUS.....					4			2		
9998 ARBO. GROUP B.					1			1		
Total.....	5	336	9	1	7	5	11	53	55	5