A Review of Literature.

A Dissertation Submitted for the Degree of

M.Sc. in Child Public Health

Institute of Child Health

University of London

August 2006

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Table of Content

Acknowledgements

I would like to thank everyone who has offered lectures to us during the course. Special thanks are due to my supervisor, Helen Bedford, for her encouragement, advice, and provision of old and unpublished papers. I particularly wish to express my appreciation to Pat Tookey, our senior lecturer, for her opinion, support, and help in finishing this thesis. I am grateful to Dr D. Fleming and Michele Barley of the RCGP, for the supply of valuable local epidemiological data, and to Nitu Sengupta, clinical research fellow, for her suggestion of key papers. I would also like to thank Carole Davis, our course administrator, Kristina Drew, deputy IT manager, and Angela Jefkins, deputy librarian, for personal lessons on Microsoft word, literature searching, and Refman. The whole course was enjoyable.

Abbreviations

BMJ	British Medical Journal
BPSU	British Paediatric Surveillance Unit
CDC	Centers for Disease Control and Prevention
CDSCNI	Communicable Disease Surveillance Centre Northern Ireland
CEMACH	Confidential Enquiry into Maternal and Child Health
CTFPHC	Canadian Task Force on Preventive Health Care
DH	Department of Health, UK
DTaP/dTaP	Diphtheria/ tetanus/ acellular pertusis vaccine
GROS	General Registered Office of Scotland
HPA	Health Protection Agency
HPS	Health Protection Scotland
Hib	Haemophilus influenzae type b vaccine
HIV	Human immunodeficiency virus infection
IPV	Inactivated polio vaccine
JCVI	Joint Committee on Vaccination and Immunisation
PCV	Pneumococcal vaccine
pfu	Plaque forming unit
PHAC	Public Health Agency of Canada
PHN	Post herpetic neuralgia
RCGP	Royal College of General Practitioners
RCOG	Royal College of Obstetricians and Gynaecologists
RCPCH	Royal College of Paediatrics and Child Health
RCT	Randomised controlled trials

Men C	Meningococcal C vaccine
MHLW	Ministry of Health, Labour, and Welfare of Japan
MMR	Measles-mumps-rubella vaccine
MMWR	Morbidity and Mortality Weekly Report
MMRV	measles, mumps, rubella, and varicella vaccine
MSGP	Morbidity Statistics from General Practice
NHS	National Health Services
NIID	National Institute of Infectious Diseases of Japan
NISRA	Northern Ireland Statistics and Research Agency
ONS	Office for National Statistics
SCIEH	Scottish Centre for Infection and Environmental Health
Td	Tetanus/ diphtheria
UK	United Kingdom
US	United States
VEARS	Vaccine Adverse Event Reporting System
VZIG	Varicella zoster immunoglobulin
VZV	Varicella zoster virus
WAES	Worldwide Adverse Experience System
WHO	Worth Health Organization
WRS	Weekly Returns Service

Throughout this thesis, the term varicella implies primary VZV infection (chickenpox) and zoster means herpes zoster. Oka/Merck is equivalent to Varivax. Oka/RIT is interchangeable with Oka/GSK or Varilrix.

Abstract

Background

Varicella (chickenpox) is a common infectious disease. It is experienced by almost every individual worldwide. Though the disease is generally mild, serious complications and even death can occur. Varicella vaccines are licensed in UK since 2002. Their potential use as routine childhood immunisation is controversial because of the uncertainty of impact on epidemiology. Nevertheless, it is becoming a more common option in developed countries. Eleven countries already included this vaccine in their national vaccination programmes to date.

Objectives

To discuss whether varicella vaccine should be included in the current UK childhood immunisation programme with reference to the local epidemiology, economic considerations, alternative strategies, concerns about vaccine issues, potential impact on epidemiology, and parental acceptability.

Method

A review of literatures.

Findings

VZV infection is an important public health concern in UK. Half UK children acquire the infection by age 5 and 85% are infected before reaching adulthood. There is £35-£223 million lost per year because of this infection. Varicella vaccines are generally well tolerated. Vaccine efficacy is 70-90% and 85-95% against disease of any severity and severe diseases respectively. Breakthrough diseases are milder. From US experience, disease burden of varicella declined after mass immunisation. However, the impact on zoster epidemiology is less certain. Moreover, varicella is perceived as a mild infection by most British parents. Even if varicella vaccine is to be offered free, only 40% parents will accept it.

Conclusion

Given the current evidences, it is not justified to include varicella vaccine to the current childhood immunisation programme of UK at the moment.

Introduction

Every country faces many different heath problems, yet resources are limited. Good utilisation of these limited resources requires setting priorities. Preventive medicine is nowadays the direction of public health in both developed and developing countries. According to the World Health Organization (WHO), "The two public health interventions that have had the greatest impact on the world's health are clean water and vaccines".(1)

Varicella (chickenpox) is a vaccine preventable disease. It is caused by varicella zoster virus (VZV) which is a herpesvirus. Clinical varicella was not reliably distinguished from smallpox until 19th century. In 1888, von Bokay found that varicella and zoster were related as susceptible children acquired varicella after contact with herpes zoster. The virus was isolated by Weller and Stoddard in 1952.(2) Only one serotype is known. Primary infection results in varicella. As with other herpes virus, VZV has the ability to reactivate later in life, leading to zoster. VZV is highly contagious with worldwide distribution. Secondary infection rate from household contacts is as high as 90%.(3) Varicella is perceived as a mild infection of children and rarely rated as an important public health concern. However, VZV infection can be associated with significant morbidity and mortality.

Varicella vaccine is the first vaccine against herpesvirus. It is also the first live attenuated vaccine to be used in both healthy and immunocompromised children.(4) Nevertheless, the need for routine immunisation in healthy children has been controversial. It is worthwhile to have a review of the current status of the use of the vaccine worldwide and to explore the possibility of mass immunisation of healthy children in UK.

Format

In UK, national immunisation policy is advised by the Joint Committee on Vaccination and Immunisation (JCVI) (**Appendix A**).(5;6) No formal guideline on how vaccination policy was decided in UK could be found from the JCVI website. Therefore, the format of this thesis will be based on the following World Health Organization (WHO) expert papers and information from the UK Immunisation Division of Communicable Disease Surveillance Centre (CDSC), Health Protection Agency (HPA).

1) Assessing new vaccines for national immunization programmes. (WHO, 2002)(7)
2) Vaccine introduction guidelines: adding a vaccine to a national immunization programme: decision and implementation. (WHO, 2005)(8)
3) General WHO position on new vaccines (Available under WHO position paper on varicella vaccine). (WHO, 1998)(9)
4) How are new vaccines introduced? (Presentation by Dr. Miller at Royal Society of Medicine Symposia: childhood immunisation, 2004, available at HPA online)(10)

Including New Vaccines in Established Programmes

In considering whether a vaccine should be added to a routine childhood immunisation programme, the following issues need to be considered:

A) Policy Issues

1) **The disease**

   Is the disease a public health concern?

   What is the disease burden?

2) **Economic considerations**

   Is the disease a burden economically?

3) **Other alternatives**

   Is immunisation the best strategy for control the disease?

4) **Vaccine issues**

   Is the vaccine efficacious and safe?

5) **Parental Acceptability**

   Is the vaccine likely to be accepted by parents?

   What is the expected vaccine coverage rate?

B) Programmatic Issues

1) Vaccine supply/ availability
2) Product selection (monovalent/ combination, single/ multiple doses)
3) Vaccine programme- may need to identify areas that need strengthening

C) Other Considerations

Possible **impact on epidemiology**

In discussing this issue for my thesis, I will only focus on the policy issues and the impact on epidemiology.

Method

This is a literature review. International expert opinions were searched through the websites of the World Health Organisation (**WHO**) (http://www.who.int/en), US Centers for Disease Control and Prevention (**CDC**) (http://www.cdc.gov), and the Public Health Agency of Canada (**PHAC**) (http://www.phac-aspc.gc.ca/new_e.html).

UK national information was searched from the websites of the National Health Services (**NHS**) (http://www.nhs.uk), Health Protection Agency (**HPA**) (http://www.hpa.org.uk), the Royal College of Paediatrics and Child Health (**RCPCH**) (http://www.rcpch.ac.uk), Royal College of General Practitioners (**RCGP**) (http://www.rcgp.org.uk), and the Royal College of Obstetricians and Gynaecologists (**RCOG**) (http://www.rcog.org.uk).

Reviews were searched from **Cochrane Library** (http://www.nelh.nhs.uk/cochrane.asp) and British Medical Journal (**BMJ**) Clinical Evidence (http://www.clinicalevidence.com). Studies were also obtained from **PubMed.** Details for each section were included in the **Appendix B.**

Some key articles were suggested by Nitu Sengupta, clinical research fellow of University of London. Old papers and some unpublished papers were kindly provided by my supervisor, Helen Bedford.

1 The Disease

WHO defined disease burden as an indicator of disease outcome, both disease epidemiology and financial issues.(11) This part thus will focus on the epidemiology of VZV infection (disease incidence, morbidity, and mortality) and economic considerations. As the disease reporting systems are different in the four countries of the UK, they will be discussed separately.

1.1 Incidence

Varicella

Statutory notification of varicella was introduced in Scotland in 1988 (12) and in Northern Ireland in 1990.(13) However, varicella is still not a notifiable disease in England and Wales.(14)

England and Wales

Though varicella is not a notifiable disease in England and Wales, information about incidence is available from both passive and active surveillance. Voluntary reports were available through the Weekly Returns Service (**WRS**) of the Birmingham Research Unit of Royal College of General Practitioners (**RCGP**) by sentinel practices.(15) Data are collected currently from approximately 100 practices well distributed across England and Wales and reported every two weeks. The incidence of varicella has been monitored since 1967.(16) There was also active surveillance, the Morbidity Statistics from General Practice (**MSGP**),

which was carried out approximately every ten years in England and Wales.(17) The latest series was the fourth series (MSGP4) which was carried out in 1991-92 and published in 1995. This series covered about 1% of total population in England and Wales in that period. All the following studies were based on data from either the WRS or the MSGP4.

By studying passive surveillance, Fleming et al reported an average incidence rate (all ages) of 250-750 and 500 per 100,000 population per year in the past 30 and 10 years respectively.(18) Annual incidence rate (age-standardised) was 420-590 per 100,000 person-years in 2001-2004 according to the 2001 annual report of RCGP (**Figure 1**).(19)

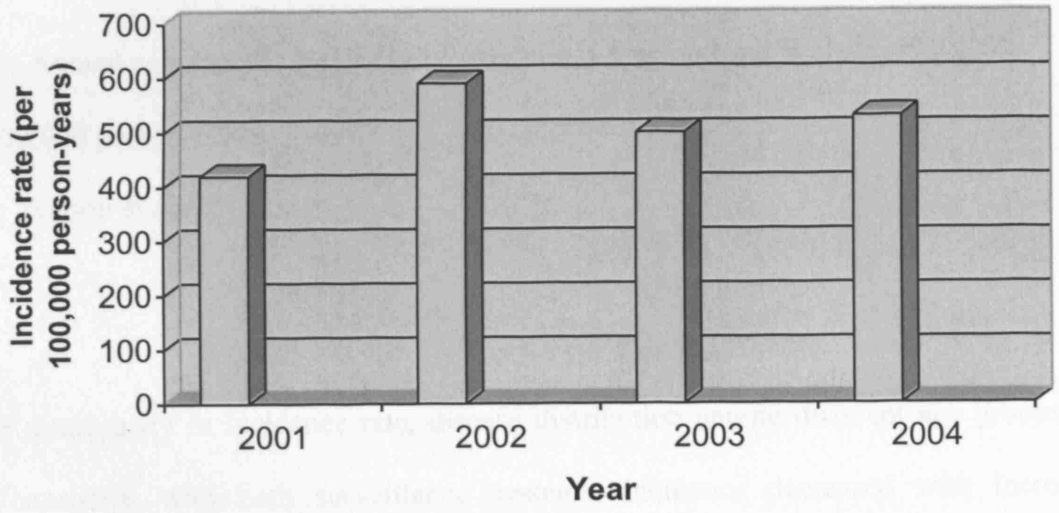


Figure 1: Age- standardised annual incidence rate (per 100,000 person-years) of varicella in England and Wales, 2001-2004.

Source: RCGP.(19)

The figure was very different if both passive and active surveillance data were included. By analysing both WRS and MSGP4 data, Brisson et al estimated that there were 670,868 new cases per year in 1991-2000.(20) Overall incidence rate was about 1,290 cases per 100,000 person-years (**Table 1**).

Age (years)	Number of cases	Incidence rate*	Proportion of all cases
0-4	344,662	10,331	51%
5-14	224,242	3,384	33%
15-44	95,730	435	14%
45-64	4,945	42	1%
≥ 65	1,289	16	0%
Overall	**670,868**	**1,290**	**100%**

Table 1: Annual age-specific incidence of varicella in England and Wales, 1991-2000.

* Per 100,000 person-years.

Source: Brisson et al.(20)

Despite discrepancy in incidence rate, disease distribution among different age groups was rather consistent with both surveillance systems. Incidence decreased with increasing age.(18;20;21)

In the study by Brisson et al, incidence rate decreased from 10,331 per 100,000 population in children 0-4 years to 435 per 100,000 population in adults 15-44years. Cases after 45 years were rare (16-42 per 100,000 population) (see Table 1 above).(20)

An active 26-week surveillance was carried out in 2000 by Fleming et al to identify secondary cases infected through household contacts.(18) The population studied was 611,000 (1.2% of total population in England and Wales in 2000)(22;22) Contacts were made to the index cases 3 weeks after presentation to identify secondary cases 3 weeks before and after the incidence cases. The final total incidence rate was estimated to be 280 per 100,000 population (**Table 2**). Total incidence rate decreased with age, from 3,110 per 100,000 population in 0-4 years to 50 per 100, 000 population in those ≥ 15 years. 14% of incident cases did not consult their GP.

Age (years)	Reported incidence rate	Total incidence rate
0-4	2,700	3,110
5-14	440	500
15+	50	50
Total	**250**	**280**

Table 2: Age-specific reported and total (reported incident cases plus secondary cases identified) incidence rate (per 100,000 population) of varicella in England and Wales, 2000. Source: Fleming et al.(18)

RCGP annual report 2004 suggested that the highest rate occurred among the 1-4 years, followed by neonates and children 5-14 years. Cases in 15-24 years and 25-44 years were roughly equal. Cases ≥ 45 years were uncommon (**Figure 2**).(21)

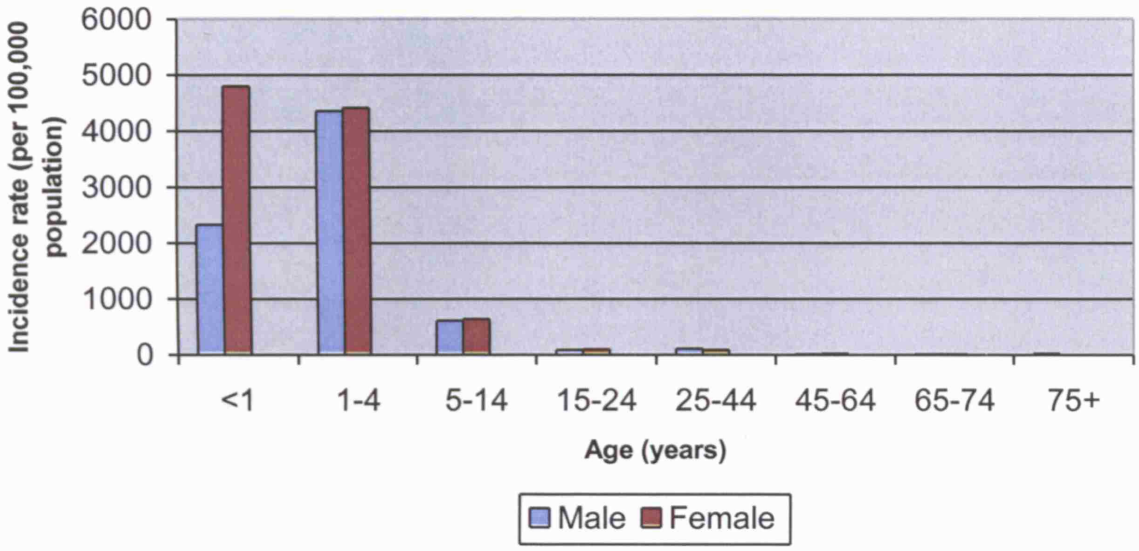


Figure 2: Age-specific annual incidence rate (per 100,000 population) of varicella in England and Wales, 2004.

Source: RCGP.(21)

In order to have more thorough information about the disease burden in England and Wales, RCGP was contacted and information on weekly mean disease episodes from 1970 to 2004 was provided.(23) This was converted to annual incidence rates and is shown in **Figure 3.** Crude annual incidences fluctuated from year to year between 250 to 640 per 100,000 population in 1970-1979, 400-700 per 100,000 in 1981-1989, and 350-650 per 100,000 population since 1990. Incidences in males and females were more or less the same and followed similar trends over years. The incidences seemed extremely high in 1980 (850 per 100,000 population). This was confirmed to be an epidemic by a study which analysed epidemiological data in 1967-1985.(24) Two epidemics were reported in this period. The other epidemic occurred in 1967. Each epidemic was followed by 2-3 years of low incidences.

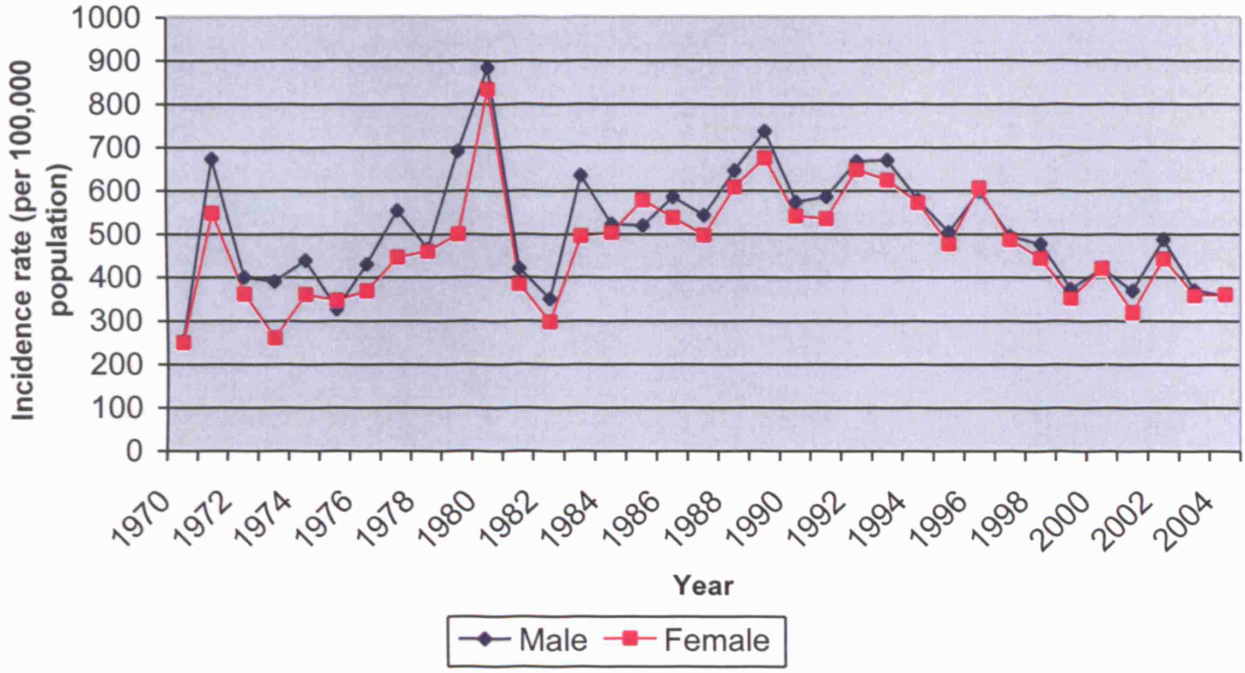


Figure 3: Annual incidence rate (per 100,000 population) of varicella in England and Wales by sex, 1970-2004. Source: RCGP.(23)

Scotland

Incidence of varicella in Scotland is available through statutory notifications to the Scottish Centre for Infection and Environmental Health (SCIEH), Health Protection Scotland (HPS).(25) The sources of surveillance in Scotland come from both clinical diagnosis and laboratory reports.(26)

An review by SCIEH reported that 23,000-40,000 new cases of varicella were notified per year in 1990-1999 (**Table 3**).(27) Much more cases of varicella were reported than other notifiable diseases.

Diseases	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999
Varicella	24587	37536	32080	40173	32851	31238	28509	33413	30181	22618
Diphtheria	0	0	0	0	0	0	2	1	1	0
Measles	2006	1701	1747	1911	6192	1307	1055	762	700	434
Meningococcal infection	216	178	207	207	201	190	201	271	313	329
Mumps	833	723	601	458	546	371	368	282	251	216
Poliomyelitis	0	0	0	0	1	0	0	0	0	0
Rubella	3702	2171	2645	2048	2916	1258	2449	818	745	548
Tetanus	2	0	1	0	1	0	2	1	0	0
Tuberculosis	563	546	559	554	546	478	509	433	457	497
Whooping cough	1291	838	236	493	639	399	186	545	225	214
Total*	**38822**	**50118**	**46251**	**51164**	**50278**	**42565**	**40161**	**42854**	**38032**	**29716**

Table 3: Notifications of infectious diseases in Scotland 1990-1999.

Source: SCIEH.(27)

* Including all notifiable diseases. Only part of the whole list is shown here.

Bramley et al estimated that there was on average 33,000 cases (range 25,000- 40,000 cases) notified each year in 1981-1998.(28) This was equivalent to an annual incidence rate (all ages) of about 480- 790 per 100,000 person-years (**Figure 4**, page 14). European age- standardised rate ranged was 540- 900 per 100,000 person-years.

More up to date information on notified cases was obtained from the HPS. Data for 2000-2004 was available (**Table 4**).(29-33) There were about 21,000-28,000 new cases per year. Much

more notifications were received for varicella than any other notifiable diseases. In order to calculate incidence rate, population information of Scotland was extracted from the General Registered Office of Scotland (GROS) (**Table 5**).(34) The estimated incidence rate (all ages) was 410 to 560 per 100,000 population per year.

	1999*	**2000**	**2001**	**2002**	**2003**	**2004**
Varicella	22618	24669	22110	28230	20757	21051
Measles	434	395	326	405	200	253
Mumps	216	198	156	250	182	3524
Rubella	548	347	240	295	159	223
Meningococcal Infection	329	303	248	181	145	147
Tuberculosis	497	406	372	374	368	363
Whooping Cough	214	93	98	103	71	93
Total**	**29716**	**37545**	**33690**	**39245**	**30509**	**33862**

Table 4: Notifications of infectious diseases in Scotland, 2000-2004.

Source: HPS.(29-33)

* from SCIEH (Table 3, page 11).(27)

** Including all notifiable diseases.

Only part of the whole list is shown here.

Year	Estimated population (mid-year)	Estimated incidence rate
1999	5,119,200	442
2000	5,114,600	482
2001	5,062,011	437
2002	5,054,800	558
2003	5,057,400	410
2004	5,078,400	415

Table 5: Estimated mid-year population and crude incidence rate (per 100,000 population) of varicella in Scotland, 1999-2004.

Source of data for population: GROS.(34)

Combining all the findings, incidence rate (all ages) of varicella in Scotland in 1989-2004 is shown in **Figure 4**. Crude incidence rate decreased through time, from 480-790 per 100,000 population to 410-560 per 100,000 in 1999-2004. Incidence was not exceptionally high in any single year.

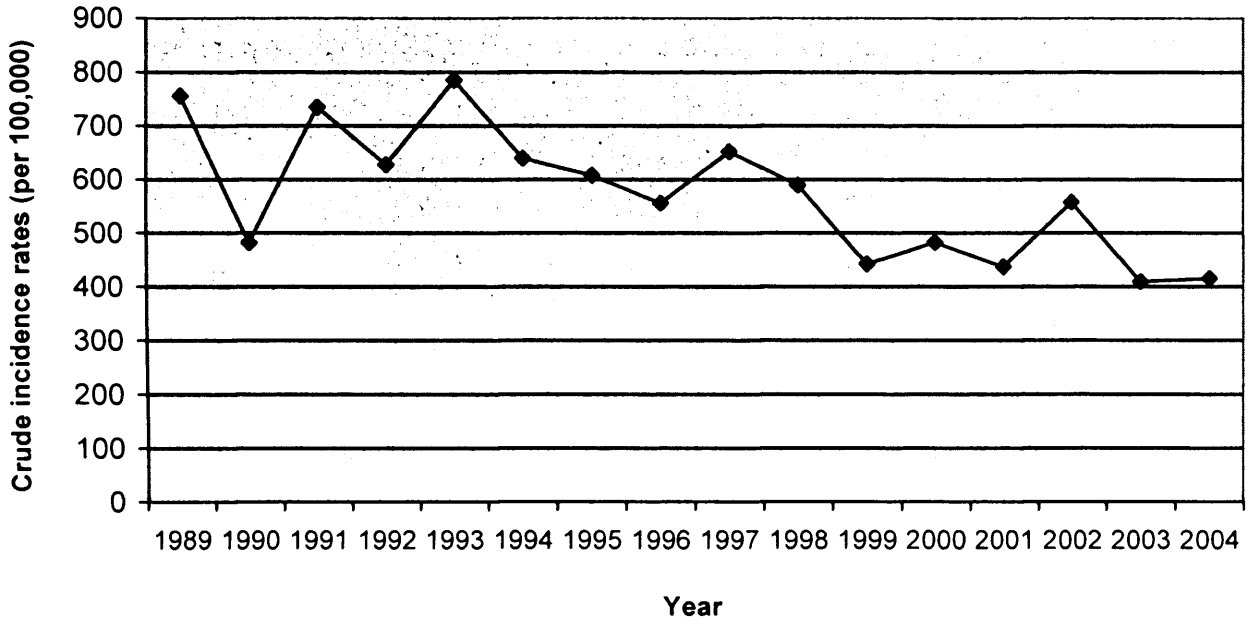


Figure 4: Estimated crude incidence rate (per 100,000 population) of varicella in Scotland, 1989-2004.

Source of incidence rate 1989-1998: Bramley et al(28)

Source on notification: SCIEH (year 1999)(25) and PHS (year 2000-2004)(29-33)

Source on population: GROS (year 1999-2004)(34)

Northern Ireland

In Northern Ireland, varicella is notified through the Communicable Disease Surveillance Centre (CDSC, NI).(35) The number of cases of varicella notified in Northern Ireland in 1990-2005 was obtained (**Table 6**).(36) As in Scotland, much more cases of varicella were reported than other notifiable diseases. Annual incidence ranged from 4,000 to 7,000 cases in recent 10 years. No data on incidence rate was available on CDSC (NI). In order to estimate incidence rate, information on population of Northern Ireland was searched from the official

website of Northern Ireland Government, the Northern Ireland Statistics and Research Agency (NISRA).(37) Only data on total population was available. No data for population distribution on age could be found. Information for the year 1990-2005 was extracted (**Table 7**).(38) Annual crude incidence rate was calculated and shown in **Figure 5**. Annual incidences ranged between 200-400 per 100,000 population except 1992. This was possibly an epidemic but could not be confirmed by study.

Disease	90	91	92	93	94	95	96	97	98	99	00	01	02	03	04	05
CHICKENPOX *	2744	3578	9955	6699	6138	4785	7004	5253	4907	4584	4531	3927	4931	4459	3768	3227
Encephalitis/ Meningitis *	158	172	118	123	144	116	105	91	64	99	130	97	98	78	64	66
Hepatitis *	313	440	304	295	267	122	79	56	108	78	46	23	11	40	59	74
Malaria*	4	8	14	8	6	5	14	16	23	13	11	13	2	1	5	2
Measles	334	342	303	495	950	263	197	120	112	79	92	96	89	57	90	56
Meningococcal septicaemia*	2	23	27	34	39	42	67	56	87	145	123	90	98	76	82	66
Mumps**	187	189	156	115	103	93	67	68	79	93	1006	537	77	180	780	4556
Paratyphoid Fever	0	0	1	1	2	0	0	1	1	0	0	0	1	0	0	0
Polio	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Rubella**	543	357	293	528	408	220	190	127	111	73	62	65	50	34	39	31
Scarlet Fever	772	575	525	575	519	502	478	425	486	432	310	283	214	304	228	186
Tetanus	0	0	0	0	1	0	0	1	0	0	0	1	0	0	0	0
Tuberculosis	131	96	84	90	93	90	75	75	61	61	58	48	68	38	73	68
Typhoid	3	0	0	1	0	0	1	1	2	0	0	1	3	0	0	1
Typhus	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Whooping Cough	285	240	205	134	234	131	148	135	100	108	61	65	69	40	28	28

Table 6: Notifications of infectious diseases in Northern Ireland, 1990-2005.

*Only notifiable from 16 April 1990. ** Only notifiable from October 1988.

Source: CDSC (NI).(36) Only part of whole list is shown here.

Year	Estimated population*	Crude incidence rate**
1990	1,595,600	172
1991	1,607,300	223
1992	1,623,300	613
1993	1,635,552	410
1994	1,643,707	373
1995	1,649,131	290
1996	1,661,751	421
1997	1,671,261	314
1998	1,677,769	292
1999	1,679,006	273
2000	1,682,944	269
2001	1,689,319	232
2002	1,696,641	291
2003	1,702,628	262
2004	1,710,322	220
2005	1,724,408	187

Table 7: Estimated crude incidence rate (per 100,000 population) of varicella in Northern Ireland, 1990-2005.

Source of data on population: NISRA.(37)

* Mid-year estimation.

* * Per 100,000 population.

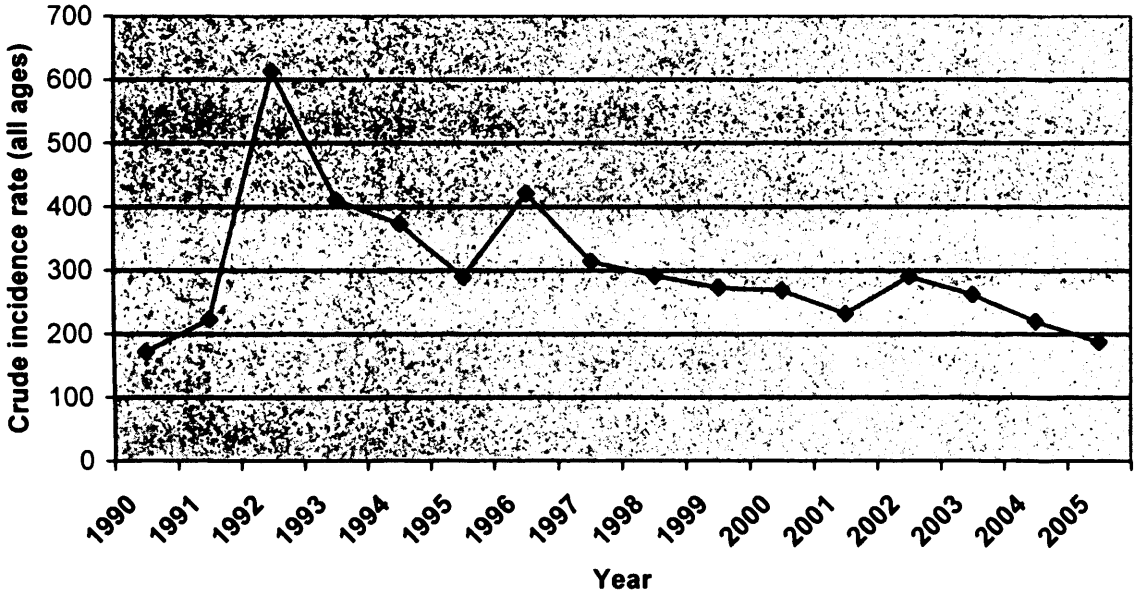


Figure 5: Crude incidence rate (per 100,000 population) of varicella in Northern Ireland, 1990-2005.

Source: CDSCNI and NISRA.(35;37)

Zoster

Herpes zoster is not a notifiable disease in any of the four countries in UK.(12-14)

As it is not notifiable, a few assumptions have to be made in order to estimate the incidence of the disease;

- Zoster consultation rate is used to estimate the incidence rate. This is because of the severity of zoster, all individuals with zoster are assumed to consult their general practitioners. (20)
- All individuals suffer zoster only once in their lifetime.(39)

The following studies obtained their data from either WRS of RCGP (zoster data was available since 1967) or MSGP4.

Lifetime risk of developing zoster was 23-30% among UK populations.(16;40;41) Before 1993, 194,000 new cases were diagnosed each year.(41) In 1967-1992, incidence rate (all ages) was about 400 per 100,000 population.(16) In 1990s, there were about 225,000 new cases per year. Average annual incidence rate (all ages) was 370-400 per 100,000 person-years.(20;39) In 2001-2004, age-standardised prevalence rate (defined as persons consulting on one or more occasions during the year) was reported to be 450-480 per 100,000 person-years by RCGP (**Table 8**).(19)

Year	Incidence rate
2001	450
2002	450
2003	480
2004	470

Table 8: Age-standardised annual prevalence rate (per 100,000 person-years) of zoster in England and Wales, 2001-2004.

Source: RCGP.(19)

On the contrary to varicella, incidence rate of zoster increased with age.(16;20;39-42) Before 1993, there were on average 100-200, 200, 800, and 1,000 per 100,000 person-years of cases in the age groups < 15 years, 15-44 years, ≥ 65 years, and ≥ 85 years respectively (**Figure 6**). Incidence after 45 years old rose rapidly, with an average of 1.45 episodes of zoster during whole lifetime.(16;41)

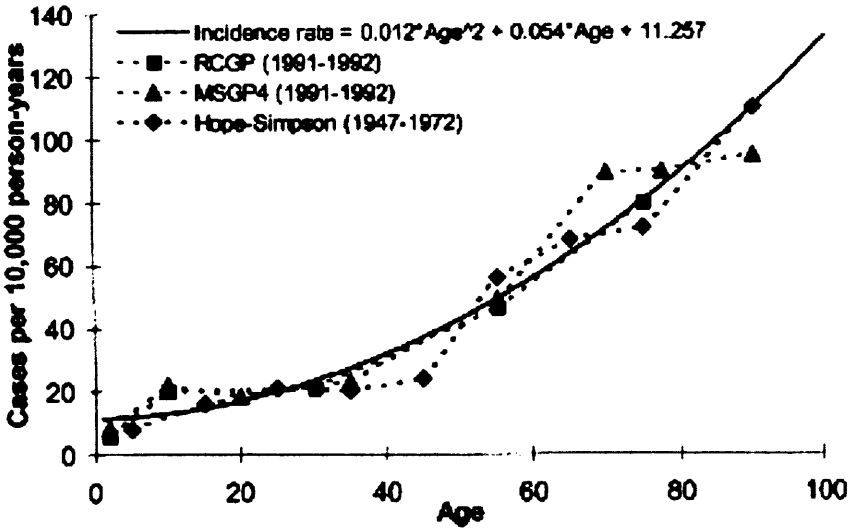


Figure 6: Age- specific annual incidence rate (per 10,000 person-years) of zoster in England and Wales, 1947-1972, 1991-1992. Copied from Edmunds et al.(41)

Studies in 1980s-1990s reported similar findings.(20;40;42) Incidence rate was 80-90 per 100,000 person-years for children 0-4 years and 200 per 100,000 person-years for both groups 5-14 years and 15-44 years. After 45 years of age, risk increased dramatically to 500-1,000 per 100,000 person-years (**Table 9, 10** and **11**). Children 0-14 years and adults ≥ 45 years accounted for 7-9% and 60- 70% of all cases respectively.

Age (years)	Incidence rate	Proportion
0-4	76	
5-14	179	9%
15-44	210	31%
45-64	470	
≥ 65	771	60%

Table 9: Age- specific incidence rate (per 100,000 person- years) of zoster in England and Wales, 1979-1997. Source: Brisson et al.(40)

Age (years)	Number of cases	Incidence rate*	Proportion
0-4	3,081	92	1%
5-14	14,537	219	6%
15-44	46,760	212	21%
45-64	83,674	712	37%
≥ 65	76,766	932	34%
Overall	**224,818**	**373**	**100%**

Table 10: Annual age- specific incidence of zoster in England and Wales, 1991-2000.

* Per 100,000 persons years.

Source: Brisson et al.(20)

Age (years)	**Incidence rate** (per 100,000 person-years)	
	Males	**Females**
0-14	162	231
15-24	212	211
25-44	199	245
45-64	399	591
65-74	775	984
≥ 75	958	1,104

Table 11: Age-specific incidence rate of zoster in England and Wales by sex, 1994-2001.

Source: Fleming et al.(42)

Although incidence of zoster increase significantly only after 45 years of age (**Figure 7**), 10% UK population < 45 years suffered from at least one episode of zoster. This increased to 25% in those ≥ 45 years.(39)

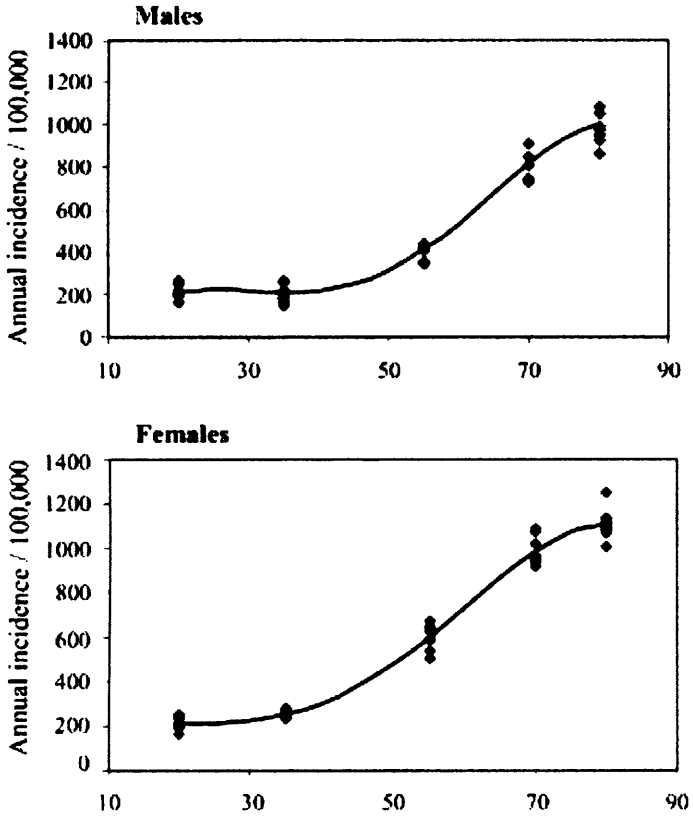


Figure 7: Annual incidence rate (per 100,000 population) of zoster in both males and females in England and Wales, 1994-2001.

Copied from Chapman et al (39)

1.2 Consultation

Varicella

Estimated consultation rate (per case) depends on the source of information. RCGP report estimated that the overall consultation rate (all ages) was 1.4 per case without giving further details on different age groups.(21) The following was an estimation of age-specific consultation rate based on different data sources.

Based on passive surveillance (WRS), consultation rate ranged from 1.4-1.8 in England and Wales in 2004 (**Table 12**).(21) Rate increased with increasing age. Overall rates (all ages) in male and female were the same. Details of calculation can be found in **Appendix C**.

Age (years)	Consultation rate
< 1	1.4
1-4	1.4
5-14	1.6
15-24	1.6
25-44	1.7
45-64	1.8
65-74	1.8
≥ 75	1.8
All ages	**1.5**
Males	1.5
Females	1.5

Table 12: Age-specific consultation rate (per case) of varicella in England and Wales, 2004. Source: RCGP.(21)

If both passive and active surveillance data (WRS and MSGP4 respectively) were included using information from Brisson et al's publication, estimated consultation rate was 0.3-0.9 per case (**Table 13**) in England and Wales. Consultation rate was lowest in the group 5-14 years, only one third attended their GP. However, in those ≥ 65 years, 9 out of 10 cases needed to consult a doctor. Details of calculation and raw data can be found in **Appendix C**.

Age (years)	Consultation rate (per case)
0-4	0.4
5-14	0.3
15-44	0.5
45-64	0.5
≥ 65	0.9
Overall	**0.4**

Table 13: Age-specific consultation rate (per case) of varicella in England and Wales, 1991-2000.

Source: Brission et al.(20)

In Scotland where varicella was notifiable, Bramley et al reported an average of 0.7 consultations per case (**Table 14**). Children had lower consultation rate than adults. Details of calculation and raw data can again be found in **Appendix C**. No information about consultation rate of Northern Ireland could be found.

Age (years)	1996	1997	1998
< 1	0.8	0.7	0.7
1-4	0.8	0.7	0.7
5-14	0.7	0.6	0.6
15-24	1.3	1.1	1.1
45-64	2.4	1.2	1.8
≥ 65	1.5	1.2	1.5
All ages	**0.8**	**0.7**	**0.7**

Table 14: Age-specific consultation rate (per case) of varicella in Scotland, 1996-1998. Source: Bramley et al.(28)

* Consultation rate for the group 25-44 years could not be calculated. See **Appendix C** for explanation.

Zoster

As most studies were based on the assumption that every zoster case consulted their GPs, very few publications investigated the real consultation rate. Edmunds et al used both WRS and MSGP4 and reported that on average every episode of zoster resulted in 1.45 GP consultations in England and Wales.(41)

1.3 Complication

Varicella

Primary varicella is in general a mild and self limiting disease in children. Possible complications include secondary bacterial infections of the vesicles, pneumonia, and central nervous involvements (such as meningitis, encephalitis, and cerebellar ataxia). Rare complications include Reye syndrome, Guillain-Barre syndrome, thrombocytopenia, and haemorrhagic varicella. In US, invasive group A streptococcal infections complicating varicella have been described with increased frequency.(43;44) The following findings were based on UK populations or studies.

In Children

The most common complication seen in children is secondary bacterial skin infection with staphylococci or streptococci. Reye's syndrome is now rare as aspirin no longer used in children.(45) A one-year surveillance by the British Paediatric Surveillance Unit (BPSU) reported a total of 159 severe complicated varicella cases in 2002-2003 in children under 16 years in UK (all four countries).(46) At least 107 of these cases had been confirmed to be due to varicella (**Figure 8**). This study included all children less than 16 years who suffered from complications or deaths secondary to varicella or were admitted to paediatric intensive care units (ICU) or high dependency units (HDU) with varicella or one of its complications. Pneumonia was the commonest complication, followed by bacteraemia and encephalitis (**Table 15**). Eventually 5 children died, aged $\leq$ 1 month, 1 year, 3 years, 10 years, and 14 years.

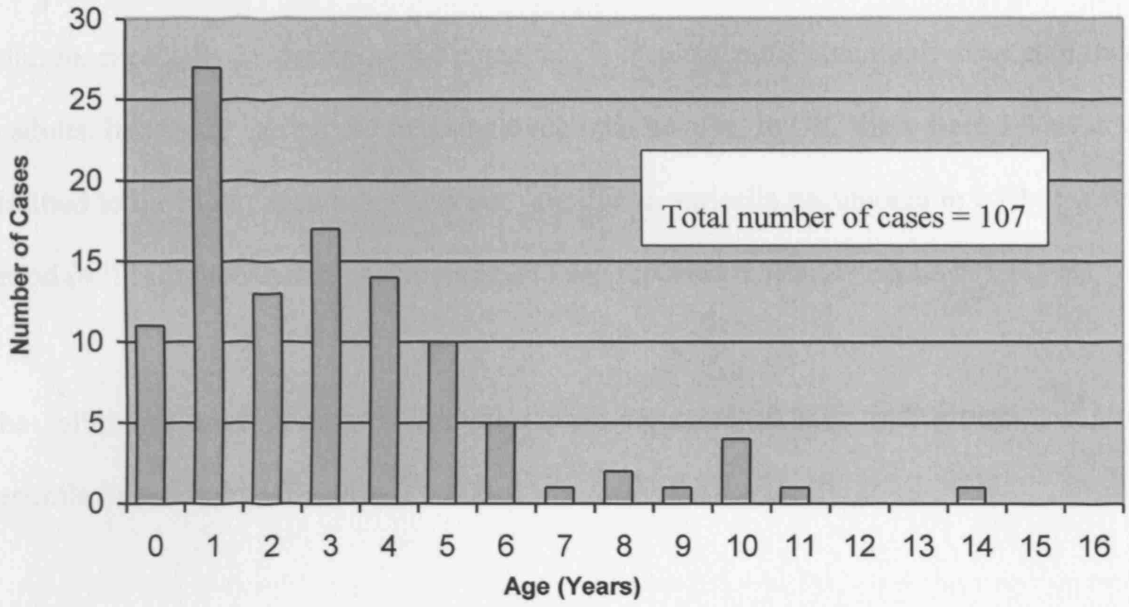


Figure 8: Confirmed cases of complicated varicella in UK in children less than 16 years of age, 2002-2003.

Source: BPSU.(46)

Clinical diagnosis	Frequency
Pneumonia	29
Bacteraemia	27
Admitted to ICU/HDU	27
Encephalitis	25
Ataxia	17
Septic shock, TSS/ Toxin mediated disease	10
Necrotising fasciitis	6
Purpura fulminans/ DIC	5
Fulminant varicella	5
Death	5
Neonatal varicella	3
Reye's syndrome	0
Total	**159**

Table 15: Reported complicated varicella cases in UK in children under 16 years, 2002-2003.

Source of data: BPSU.(46)

TSS: toxic shock syndrome DIC: disseminated intravascular coagulopathy

In adults

Varicella is generally more severe and complications more commonly seen in adults than in children, especially in smokers.(3) Pneumonia is also the most commonly seen complication in adults. In a study carried out in a single regional hospital in UK, there were 3-4 adult cases admitted to the high dependency unit per year due to varicella pneumonia in a 10-year review period.(47) Life threatening pneumonia had been reported in healthy adults in UK.(48)

The following three groups of individuals are regarded as high risk groups for primary varicella infection by HPA.(43)

1) Pregnant Women

Based on the fact that 90% adults raised in the UK were immune to VZV infection, it was estimated that less than 10% women at reproductive age in UK were susceptible to VZV infection.(3)

Risk in Mother:

Pneumonia is again the major complication for women acquiring primary varicella during pregnancy. It occurs in up to 10% of pregnant women with varicella and is more likely to be fulminant, with case fatality rate of 0.1-1% in UK.(3;49) The severity of this complication increases with increasing gestation. A guideline from the Royal College of Obstetricians and Gynaecologists (RCOG) reported that acute varicella infection during pregnancy resulted in 9 deaths in 1985-1996 in UK (**Table 16**).(49) All deaths were due to pneumonia. More information on maternal mortality was obtained from the national confidential enquiry of UK, the Confidential Enquiry into Maternal and Child Health (CEMACH).(50) There was one death in 1994-1996 and another one in 1997-1999 secondary to varicella pneumonia, out of a

total of 9 and 13 fatal maternal infections respectively.(51;52) No maternal death secondary to varicella was reported from 2000 to 2002.(53) The surveillance programme was dissolved since March 2003. No more data can be found since then.

Year	Deaths due to varicella	Total deaths*
1985-1993	8	Unknown
1994-1996	1	9
1997-1999	1	13
2000-2002	0	14

Table 16: Maternal deaths due to infections during pregnancy in UK, 1985-2002.

* Included only deaths secondary to infections during pregnancy.

Source: RCGP (49) and CEMACH.(51-53)

Risk in Fetus:

Risk depends on the gestation age the mother acquires primary infection.(49;54)

- **In the first half of pregnancy,** the risk to the fetus is congenital varicella syndrome. This consists of microcephaly, hypoplasia, cataracts, growth retardation and skin scarring. The risk is around 1-2% in the first 20 weeks in a large scale join study in UK and Germany.(55)
- **In the second half of pregnancy,** the main complication to the fetus is development of zoster in otherwise healthy children in the first few years of life. This is believed to be due to reactivation of VZV infection in utero. If maternal infection occurs 1-

4 weeks before delivery, a third of newborn infants develop clinical varicella despite the presence of acquired maternal antibody.

- **In the week before to the week after delivery,** there is a chance of severe and even fatal clinical varicella in neonates, owing to the lack of maternal antibody.

The UK rubella vaccination policy since 1970, to provide protection to individual women and then after 1988, to eliminate rubella by immunising all children using MMR vaccine, means that varicella infection in pregnancy is currently more common than rubella in UK.(56) The risk of infection during pregnancy was estimated to be 2-3 infections per 1000 pregnancies (or 2000 maternal infections per year) in England and Wales (based on use of varicella zoster immunoglobulins in pregnant women in 1996-1999).(54) Case fatality of congenital varicella syndrome was estimated to be 1 in 6 and there were about 9 infants died of this complication per year in 1989-90 in UK.(16) **Table 17** is a summary of characteristics of both gestational varicella and rubella infections in UK. Congenital abnormalities have not been reported following maternal varicella after 20 weeks' gestation in UK.(49) However, severe deformity had been documented as late as 26 weeks in Australia.(57)

	Varicella	Rubella
Susceptible population	10%	1-2%
Number of infections	2-3 cases per 1,000 pregnancies or 2000 cases per year (1996-99)	Now rare
Infectivity after close contact	High (70-90%)	High (90%)
Incubation period	14-21 days	14-21 days
Infectivity period	2 days pre onset of rash until vesicles crust	7 days pre to 10 days post onset of rash
Adverse outcome for mother	Pneumonia (case fatality 0.1-1%)	Arthritis
Risk of intrauterine transmission (by gestation age)	<28 weeks 5-10% 28-36 weeks 25% >36 weeks 50%	<11 weeks 90% 11-16 weeks 55% >16 weeks 45%
Adverse fetal outcome	< 20 weeks 1-2% congenital varicella syndrome 20-36 weeks risk of develop zoster in early childhood 36-39 weeks 50% fetus infected and 20% develop clinical varicella after birth 1 week pre and post delivery risk of life threatening neonatal varicella	<11 week 90% 11-16 weeks 20% 16-20 weeks minimal > 20 weeks no known increased risk
Babies born with congenital abnormalities	1989-1990 9 cases per year (estimated)	1994-96 19 cases 1997-2002 1 case (proven)
Termination of pregnancy	8 cases in Scotland 1981-1998 Others periods/ areas unknown	1995-96 18 cases 1997 2 cases

Table 17: Characteristics of varicella and rubella infections during pregnancy in UK.

Source: Bramley et al, Morgan-Capner et al, and RCOG.(28;49;54)

2) Neonates

Risk to the neonate includes pneumonia, severe disseminated or haemorrhagic varicella.(3)

3) Immunocompromised Individuals

In immunocompromised people (e.g. HIV, malignancy, transplant recipients, people receiving chemotherapy), varicella tends to be severe. There is increased risk of severe disseminated disease.(3)

Zoster

Post herpetic neuralgia (PHN) is the most common complication of zoster.(58) It is persistent pain after zoster (59) and can persists for years after the rash subsides.(43) About 15% individuals with zoster in England and Wales develop PHN. Risk increases with age, rises from nearly zero in those less than 30 years to over 30% in those over 80 years old. A UK study estimated that PHN lasted for about 1.4 years (range 0.9 to 2 years).(41)

RCOG stated that localised zoster in pregnancy did not appear to cause foetal abnormalities.(49) However, it was uncertain whether disseminated zoster, as seen in immunocompromised, carried a risk.(54)

1.4 Hospitalisation

Varicella

Brisson et al reported that overall admission rate was 4.5 per 100, 000 person-years, or 0.3 per 100 cases in England and Wales in 1995-1996 (**Table 18**).(20) Absolute number of admission and hospitalisation per 100,000 population decreased with age, signifying decrease in incidence with age. However, admission rate per 100 cases and length of stay both increased with increasing age, reflecting the fact that varicella is more severe with advancing age (except the group 5-14 years who had the lowest admission rate per case). Admission rate (per 100 cases) was 31 times higher and length of stay 3.5 times longer in adults over 65 years than in children 5-14 years. Majority (95%) of people hospitalised were healthy individuals without any underlying diagnosis (**Table 19**).

Miller et al and Bramley et al estimated that hospitalisation rate (all ages) was 2.4-9.9 per 100,000 population in Scotland in 1981-1998.(16;28) Greater severity of varicella in adults was again reflected by increased proportion of cases requiring hospitalisation with increasing age. Less than 1% of all cases in children 0-14 years were admitted. This proportion rose to 2% in adults 15-44 years and to 6% in those $\geq$ 45 years.(16)

Age (years)	No. of cases hospitalised (proportion)	Hospitalisation rate*	Hospitalisation rate (per 100 cases)	Length of stay (days)
0-4	1,240 (57%)	38.7	0.4	2.2
5-14	287 (13%)	4.6	0.1	3.0
15-44	560(26%)	2.7	0.6	4.0
45-64	64 (3%)	0.6	1.4	5.8
≥ 65	38 (2%)	0.5	3.1	10.6
Total	**2,189 (100%)**	**4.5**	**0.3**	**3.0**

Table 18: Varicella related hospitalisation in England and Wales by age, 1995-1996.

* Per 100,000 person- years admitted. Source: Brisson et al.(20)

Underlying diagnosis	Number	Proportion of all admission
HIV* infection	5	0.2%
Malignancies	81	3.7%
Agranulocytosis	11	0.5%
immune disorders	9	0.4%
Cystic fibrosis	10	0.5%
Total	**116**	-
At least had one underlying diagnosis	106	4.8%
Deaths	9	0.4%

Table 19: Underlying diagnosis and deaths among individuals hospitalised with varicella in England and Wales, 1995-1996.

* HIV: Human immunodeficiency virus infection. Source: Brisson et al.(20)

Zoster

Overall admission rate was estimated to be 4.4 cases per 100,000 person-years, or 120 per 100 cases in England and Wales in 1995-1996 by Brisson et al (**Table 20**).(20) Hospitalisation rate (both per 100,000 population and per 100 case) was highest in those $\geq$ 65 years. Length of stay increased with age, reflecting that zoster was more severe with increasing age. About 70% of all admitted cases were adults over 65 years of age. Admission rate (per 100 cases) was 3 times higher and length of stay 4 times longer in adults over 65 years than in children 5-14 years. Again, majority (92%) were healthy individuals without any underlying diagnosis (**Table 21**).

Another study by Edmunds et al also reported that both hospitalisation rate and length of stay with increased with age.(41) Elderly over 80 years old who had zoster were 12 times more likely to be admitted and stayed 4 times longer than children (20 days versus 5 days) in 1995-96. 11% of hospitalisations were due to PHN.

Age (years)	No. of cases hospitalised (proportion)	Hospitalisation rate*	Hospitalisation rate (per 100 cases)	Length of stay (days)
0-4	40 (2%)	1.2	110	3.5
5-14	86 (4%)	1.4	70	3.4
15-44	222 (10%)	1.1	50	4.6
45-64	327 (15%)	3.0	60	5.2
≥ 65	1,473 (69%)	19.1	230	13.5
Total	**2,148 (100%)**	**4.4**	**120**	**10.8**

Table 20: Zoster related hospitalisations in England and Wales by age, 1995-1996.

* Per 100,000 person-years admitted. Source: Brission et al.(20)

Underlying diagnosis	Number	Proportion of all admission
HIV* infection	11	0.5%
Malignancies	154	7.2%
Agranulocytosis	3	0.1%
Immune disorders	4	0.2%
Cystic fibrosis	5	0.2%
Total	**177**	-
At least had one underlying diagnosis	164	7.6%
Deaths	52	2.4%

Table 21: Underlying Diagnosis and deaths among individuals hospitalised with zoster in England and Wales, 1995-1996. * HIV: Human immunodeficiency virus infection.

Source: Brisson et al.(20)

1.5 Mortality

The following studies were based on Office for National Statistics (ONS) data.(60)

Varicella

Miller et al reported that 70% of all deaths in 1985-1990 occurred in adults. 73% were immunocompetent individuals.(16) There were about 25 deaths per year in this period.

Brisson et al also reported that on average 25 people died from varicella each year in 1993-2000 (**Table 22**).(20) Average annual mortality rate was 0.05 per 100,000 person-years. Case fatality rate was dependent on age. It rose from 1 per 100,000 cases in children 0-14 years to nearly 700 per 100,000 cases in those ≥ 65 years. Overall case fatality was 4 per 100,000 cases. Adults (≥ 15 years) accounted for about 85% of all deaths.

Age (years)	No. of cases	No of deaths (proportion)	Mortality rate# (proportion)	Case fatality rate**
0-4	344,662	3 (10%)	0.08	1
5-14	224,242	1 (5%)	0.02	1
15-44	95,730	9 (35%)	0.04	9
45-64	4,945	4 (14%)	0.03	73
≥ 65	1,289	9 (35%)	0.11	689
Total	**670,868**	**25* (100%)**	**0.05**	**4**

Table 22: Annual age-specific incidence and mortality of varicella in England and Wales, 1993-2000. * Average number of deaths per year. # Per 100,000 person-years.

* *Per 100,000 cases. Source: Brisson et al.(20)

Rawson et al reported that there were 25 deaths per year from varicella in 1995-1997.(61) Overall case fatality rate was estimated to be 9.07 per 100,000 cases (**Table 23**). Fatality rate was dependent on age. It rose from 1-3 per 100,000 cases in children 0-14 years to over 700 per 100,000 cases in adults > 65 years.

Age (years)	No. of Cases #	No. of deaths*	Proportion of all deaths	Case fatality rate**
0-4	456,444	12	16%	2.6
5-14	211,930	2	2.5%	0.9
15-44	144,597	29	38.5%	20.0
45-64	11,056	11	15%	99.5
≥ 65	2,854	21	28%	735.8
Total	**826,881**	**75**	**100%**	**9.07**

Table 23: Age-specific number of cases, deaths and estimated case fatality rate (per 100,000 cases) of varicella in England and Wales, 1995-1997.

Total number of cases in 3 years.

* Total deaths in 3 years.

** Per 100,000 cases.

Source: Rawson et al.(61)

Estimated case fatality rate was much higher in the study by Rawson et al (9.07 per 100,000 cases in 1995-1997)(61) than that reported by Brisson et al (4 per 100,000 in 1993-2000).(20) Some authors believed that the finding of Rawson et al was misleading because mortality was exceptionally high in 1995-1997 and total number of death was actually decreasing, from 32 in 1996 to 18 in 2000.(62) The reason for this exception was not clear.

However, Noah et al believed that there was a true rise in mortality even if the exceptionally high death rate in 1995-97 was taken into account.(63) The authors reviewed mortality data in longer period (1985-1997) and reported that case fatality was 9.22 per 100,000 cases (**Table 24**). Annual deaths were relatively stable at an average of 26 per 100,000 population per year except two years, 1989 (19 deaths) and 1996 (39 deaths).

Year	No of cases #	No of deaths	Case fatality rate*
1985	544	25	9.19
1986	556	25	8.98
1987	514	24	9.28
1988	621	30	9.56
1989	699	19	5.36
1990	552	24	8.55
1991	554	24	8.48
1992	653	27	8.06
1993	643	30	9.07
1994	623	23	7.15
1995	484	22	8.77
1996	597	39	12.56
1997	486	20	7.88
Average	**579**	**26**	**9.22**

Table 24: Annual number of cases, deaths, and case fatality rate of varicella in England and Wales, 1985-1997.

Per 100,000 population.

* Per 100,000 cases.

Source: Noah et al.(63)

In order to have a clearer picture of the possible changing mortality in UK, more up to date mortality data was obtained from the mortality statistics on ONS. Data for 1999-2004 was available in the series DH2.(64) Total number of deaths ranged from 12 to 20 per year (**Table 25**). This was lower than that reported in 1996 (32 deaths). Adults ≥ 45 years accounted for 50- 75% of all deaths every year except 2004 in which year there was a reduction of proportion to 39% in this group. There was a rise of deaths in children 0-4 years from 0-17% in 1993- 2003 to 33% in 2004. Whether this shift persisted to 2005 was still unknown.

	93-00*	99	00	01	02	03	04
<1		1	1	1	0	0	2
1-4	3	1	1	1	0	1	4
5-14	1	1	0	0	1	1	1
15-24		1	1	0	0	0	1
25-34		1	3	1	2	1	1
35-44	9	4	2	0	1	2	2
45-54		1	2	0	2	1	1
55-64	4	3	2	1	4	5	0
65-74	9	2	4	1	2	4	3
≥ 75		3	4	7	1	5	3
Total	**25**	**18**	**20**	**12**	**13**	**20**	**18**

Table 25: Age-specific annual deaths of varicella in England and Wales, 1993-2004.

* Estimated average number of deaths per year.

Source: Brisson et al (years 1993-2000) and ONS (years 1999-2004).(20;65-70)

Zoster

Edmunds et al reported that zoster related deaths increased with age in 1985-1999.(41) Case fatality rate increased from 40 per 100,000 cases in individuals under 60 years to 200- 400 per 100,000 cases in those over 60 years. Mortality declined since mid 1990s presumably because of improvement in medical treatment. There were on average 44 deaths per year in 1995-1999.

Brisson et al found that there were 49 deaths per year (0.09 per 100,000 person-years) in 1993-2000.(20). The number of deaths declined from 64 deaths per year in 1993-1994 to 40 deaths per year in 1999-2000. Mortality rate and case fatality rate increased with increasing age (**Table 26**).

Age (years)	No. of cases*	No of deaths	Mortality rate** (proportion)	Case fatality rate#
0-4	3,081	0	0.000 (0%)	0
5-14	14,537	0	0.002 (0%)	1
15-44	46,760	1	0.003 (2%)	2
45-64	83, 674	2	0.014 (3%)	2
65+	76766	47	0.566 (95%)	61
Total	**224,818**	**49**	**0.094 (100%)**	**25**

Table 26: Age-specific number of cases, deaths and estimated case fatality of zoster in England and Wales, 1993-2000.

* Per 100,000 person-years. **Per 100,000 person-years.

Per 100,000 cases. Source: Brisson et al. (20)

More up to date mortality data was obtained from the ONS. Information on 1999-2004 was available from the series DH2 (**Table 27**).(65-70) There were 33-63 deaths per year. 97-100% of all deaths occurred in adults ≥ 45 years. This proportion remained relatively stable over these years. Children 0-14 years accounted for only ≤ 2 % deaths every year.

	93-00*	99	00	01	02	03	04
<1	0	0	0	0	0	0	0
1-4	0	0	0	1	0	0	0
5-14	0	0	0	0	0	1	0
15-24	1	0	0	0	1	0	0
25-34		0	0	0	1	0	0
35-44		0	0	1	0	0	0
45-54	2	1	0	0	0	0	0
55-64		1	2	2	1	1	5
65-74	47	1	0	2	1	2	9
75+		30	46	56	59	54	45
Total	**49**	**33**	**48**	**58**	**63**	**58**	**59**

Table 27: Age-specific annual deaths of zoster in England and Wales, 1993-2004.

* Estimated average number of deaths per year.

Source: Brisson et al (year 1993-2000)(20) and ONS (year 1999-2004).(65-70)

Figure 9 is a comparison of mortality from both varicella and zoster. Death per years from zoster was higher than varicella in any single year from 1993 to 2004.

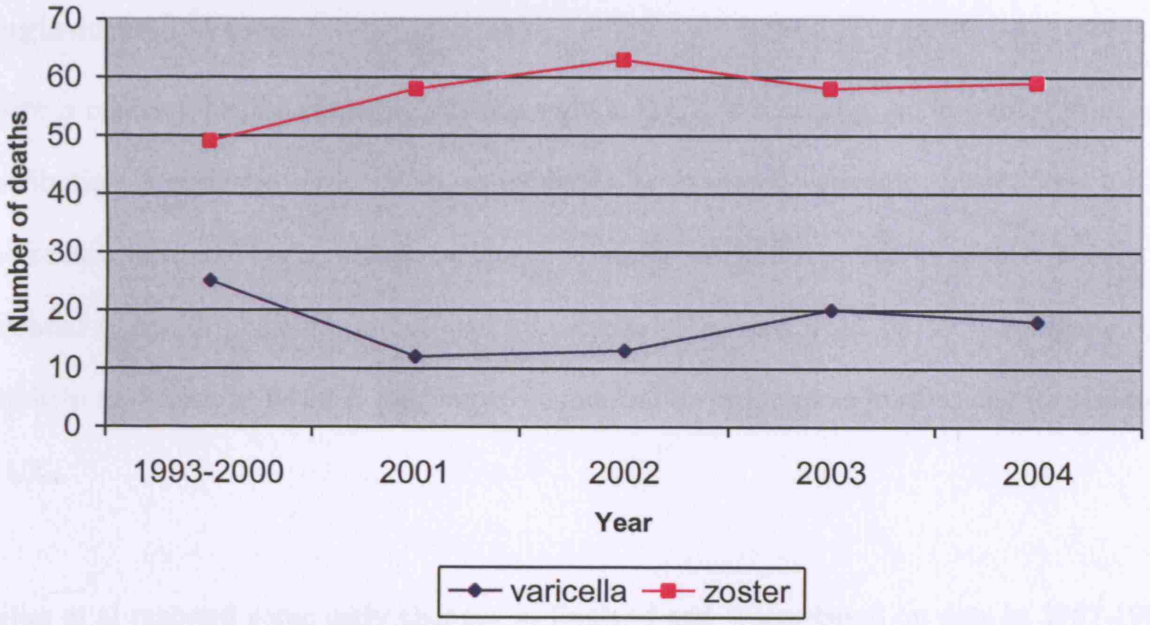


Figure 9: Comparison of annual mortality of varicella and zoster in England and Wales, 1993-2004. Source: Brisson et al (year 1993-2000), ONS (year 2001-2004).(20;65-70)

1.6 Changes in Epidemiology

Varicella

England and Wales

There is concern that the epidemiology of varicella in UK is changing. An upward shift in age distribution is observed since 1970s, as evidence by increased varicella consultations to GP and related deaths.(71) As data on incidence is important, and any shift in disease burden is essential to health planning, a thorough knowledge of current trend on VZV epidemiology will help to determine whether a universal immunisation programme is advisable for children in UK.

Miller et al reported some early changes in England and Wales based on data in 1967-1992 from WRS.(16) There was an upward shift in the reported number and proportion of varicella in adults (defined as 15 years or over). Prior to 1975, less than 10% cases occurred in adults 15-44 years. In 1989/1990, this proportion increased to nearly 20%. 40% cases occurred in children 0-4 years and another 40% in those 5-14 years. Only small number of cases occurred in those over 45 years. The incidence rates were 300 and 30 per 100,000 population in adults 15-44 years and over 45 years respectively. This upward shift of incidence was also reflected by an increase in deaths among adults. While case fatality following varicella in adults remained the same at 25 per 100,000 cases, there was a rise of proportion of total number of deaths in adults from 40% before 1970 to 70% in 1985-1990. Varicella related deaths also increased in infants 1-11 months but decreased in neonates in late 1980s compared to 1970s.

Rose et al reported data between 1970 and 1998 using the same database (WRS).(72) Before 1983, incidence rate of varicella were similar in children 0-4 years and 5-14 years. Thereafter, the rate in 0-4 years started to rise while that of 5-14 years declined. From 1983 to 1998, reported proportion doubled from 27% to 58% in children 0-4 years but halved from 52% to 24% in those 5-14 years. Incidence rate rose from 49 per 100,000 population to 86 per 100,000 population in the group 0-4 years and dropped from 40 per 100,000 population to 16 per 100,000 population in those 5-14 years. For adults 15-44 years, reported cases started to increase in 1980s and then declined in 1990s. Proportion of cases in this group declined from 26% in 1986 to 16% in 1998. Incidence rate decreased from 5 per 100,000 population in 1983 to 3 per 100,000 population in 1998.

Lowe et al studied Welsh data in 1986-2001 from GP sentinel surveillance network involving 8% (226,884) of the total Welsh population.(73) They reported a statistically significant decline in overall varicella incidence (both crude and age standardised) since 1986 ($P= 0.003$). Decline was significant in all age groups except in the youngest, 0-4 years ($P= 0.56$) (**Figure 10**). Rate in the 5-14 years declined most significantly ($P< 0.0001$) and that of individuals $\geq$ 35 years less significantly ($P< 0.003$). By using a different data source, the Welsh GP Mortality Data (GPMD) which represented 10% of total population, similar change was reported for the period 1993-2000 (**Figure 11**).

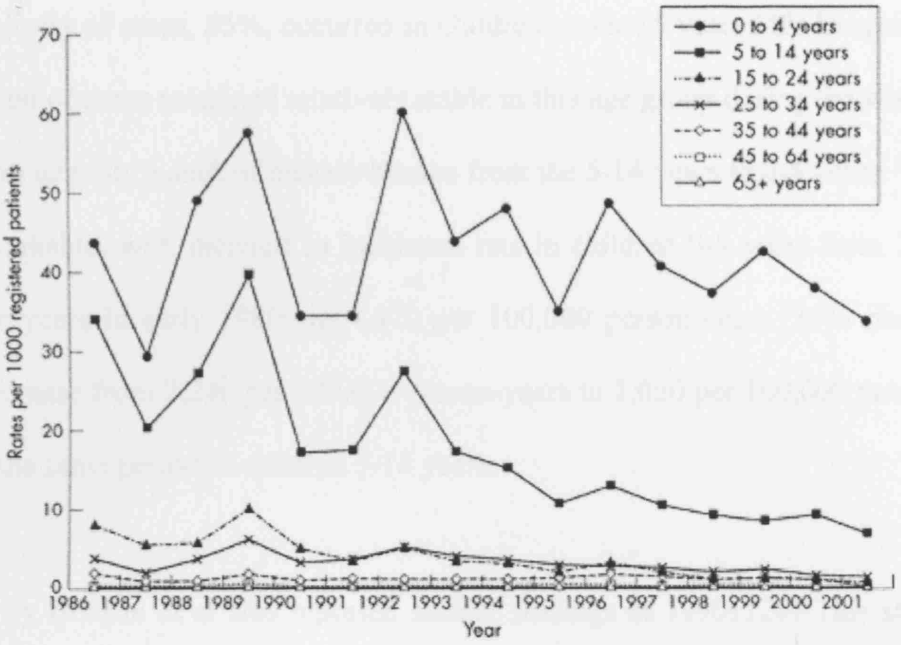


Figure 10: Age- specific incidence rate (per 1,000 registered patients) of varicella in Wales, 1986-2001.

Copied from Lowe et al, 2004.(73)

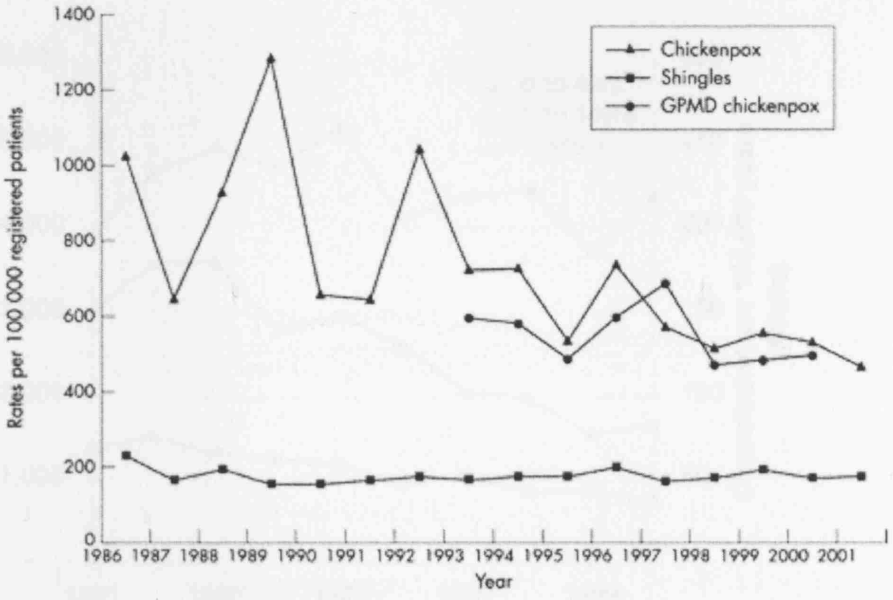


Figure 11: Age-standardised incidence rate of varicella and zoster in Wales, 1986-2001.

Copied from Lowe et al, 2004.(73)

Brisson et al reported that annual incidence rate of varicella decreased with increasing age in 1979-1997. Majority of cases, 85%, occurred in children under 15 years.(40) Despite that the overall proportion of cases remained relatively stable in this age group during the whole study period, there was actually a shift of disease burden from the 5-14 years to 0-4 years. This shift was rather remarkable, with increase in incidence rate in children 0-4 years from 3,310 per 100,000 person-years in early 1980s to 4,470 per 100,000 person-years (35% rise) in late 1990s and a decrease from 2,240 per 100,000 person-years to 1,050 per 100,000 person-years (53% drop) in the same period in children 5-14 years.

Another study by Brisson el al also reported similar findings in 1990s.(20) This study used consultation rate to examine trends in disease incidence. Annual consultation rate of varicella decreased with age (**Figure 12**). The highest rate occurred in the age group 0-4 years, average rate was nearly 4,500 consultations per 100,000 person-years. The rate in older children (5-14 years) and adults (≥ 15 years) had reduced by half in the study period.

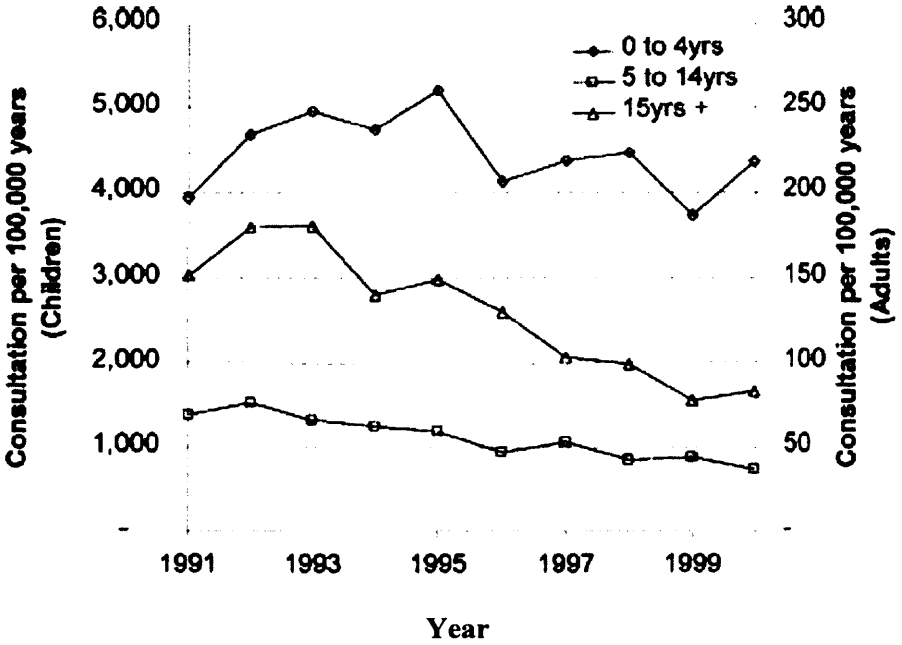


Figure 12: Annual age-specific consultation rate of varicella in England and Wales, 1991-2000. Copied from Brisson et al.(20)

More updated data was also available from the RCGP's annual reports 2001 and 2004.(19;21) Currently, highest incidence occurred in preschool children 1-4 years old (about 4,400 per 100,000 population), followed by those < 1 year (about 2,300-4,800 per 100,000 population). Incidence was rare after age 45 years (**Table 28**).

Age (years)	2001	2004	
		Male	Female
<1	2340	2336	4807
1-4	4430	4369	4432
5-14	950	610	641
15-24	140	89	99
25-44	120	109	83
45-64	20	10	21
65-74	0	10	10
≥ 75	0	21	5
All ages	**420**	**355**	

Table 28: Age- specific incidence rate (per 100,000 person-years) of varicella in England and Wales, 2001 and 2004

Source: RCGP.(19;21)

In order to analyse the disease trend over the past decades, RCGP was contacted again and age-specific information for weekly incidence rates from 1970 to 2004 was obtained. This was converted to annual rates and was shown in **Figure 13**. Before 1980s, most cases of varicella occurred in children 5-14 years, followed by children 0-4 years. From 1980-1982,

incidence rate in 0-4 years was more or less the same as that in the 5-14 years. Incidences in 0-4 years started to increase from mid 1980s and levelled off after about one decade. In recent 10 years, annual incidences in this group fluctuated around 4,000-5,000 per 100,000 population. Incidences in 5-14 years declined gradually over time. The incidence rate was about 650-900 per 100,000 population since 2000 in this group. Incidence in adult was relatively low all along. In the 15-44 years group, incidence rate increased from ≤ 150 per 100,000 population in 1970s to 150-360 per 100,000 population in 1980s. Incidence then started to decline in late 1990s and was around 100-150 per 100,000 population since 2000.

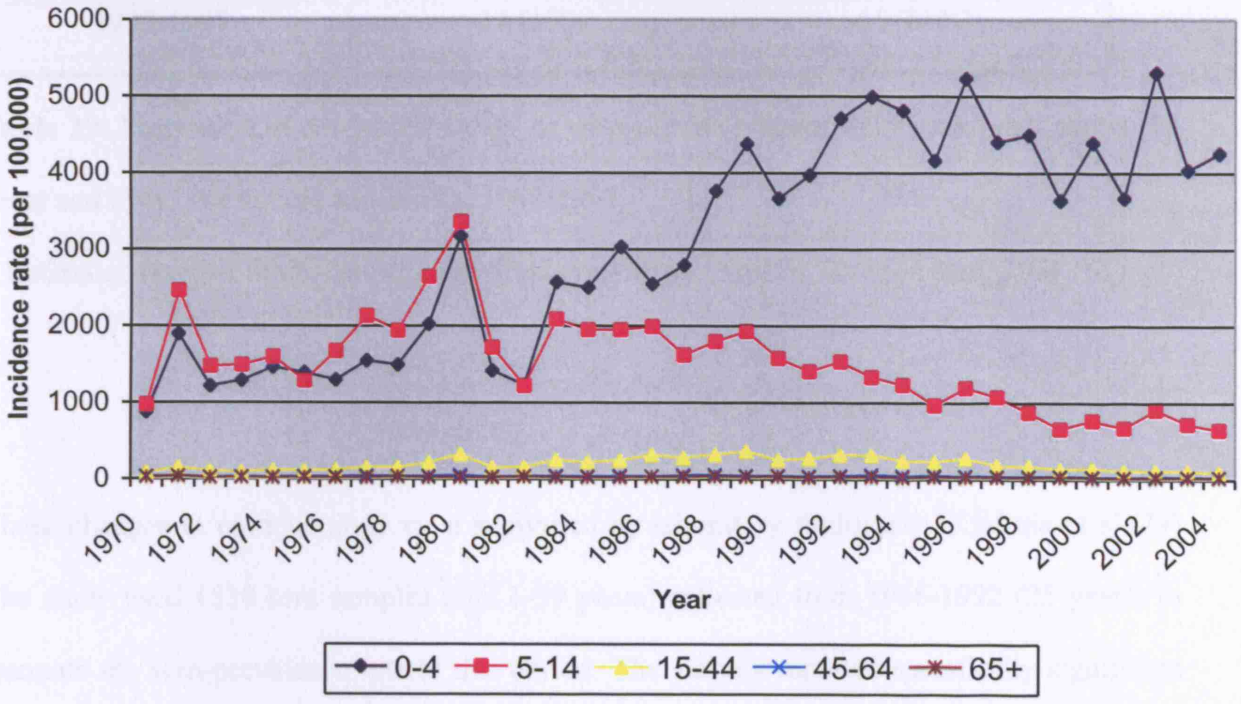


Figure 13: Annual incidence rate (per 100,000 population) of varicella in England and Wales by age group, 1970-2004. Unpublished data from RCGP.

Rawson et al reported that there was increase in varicella mortality in adults ≥ 15 years in both absolute number and proportion from 1985 to 1997 (**Table 29**). In 1967-1977, 48% of all deaths occurred in adults. This rose to 81% in 1995-1997. However, it can be seen that actually the absolute number of deaths in adults decreased from 88-269 in 1967-1995 to 61 in 1995-1997.

Year	Children	Adults
1967-1977	95* (52%)	88 (48%)
1978-1985	68* (36%)	120 (64%)
1986-1995	63* (19%)	269 (81%)
1995-1997	14 (19%)	61 (81%)

Table 29: Proportion of deaths secondary to varicella in children (0-14 years) and adults (15 years and over) in England and Wales, 1967-1997.

* Estimated number of deaths from provided proportion. Source: Rawson et al, 2001.(61)

These changes in epidemiology were supported by laboratory findings by Kudesia et al.(74) The study used 1530 sera samples (age 1-39 years) collected from 1966-1992 (25 years) to estimate the sero-prevalence rate in this period. The authors reported statistically significant differences in sero-prevalence trends over time between age groups ($p < 0.0001$) (**Table 30**). There was a remarkable increase in sero-prevalence in 1-4 year age group since late 1980s. Sero-prevalence in 20-29 years declined marginally. No significant change was observed in other age groups.

Age (years)	1966	1970	1974	1978	1984	1988	1992
1–4	7%	4%	20%	25%	24%	24%	51%
5–9	56%	65%	53%	30%	56%	35%	64%
10–19	67%	100%	83%	79%	79%	88%	96%
20–29	-	98%	99%	94%	90%	91%	92%
30–39	-	100%	91%	98%	73%	94%	96%

Table 30: Age-specific sero-prevalence (by percentage) of varicella infection in UK, 1966-1992.(74)

Scotland and Northern Ireland

For Scotland, only data for 1981-1998 was available. Bramley et al found that the incidence in children 0-4 years increased in this period (**Figure 14**).(28) Incidence in 5-24 years declined while rates in older age groups had no significant change. No information on age distribution could be found from the Scotland official sites and no age specific incidence could be found for Northern Ireland.

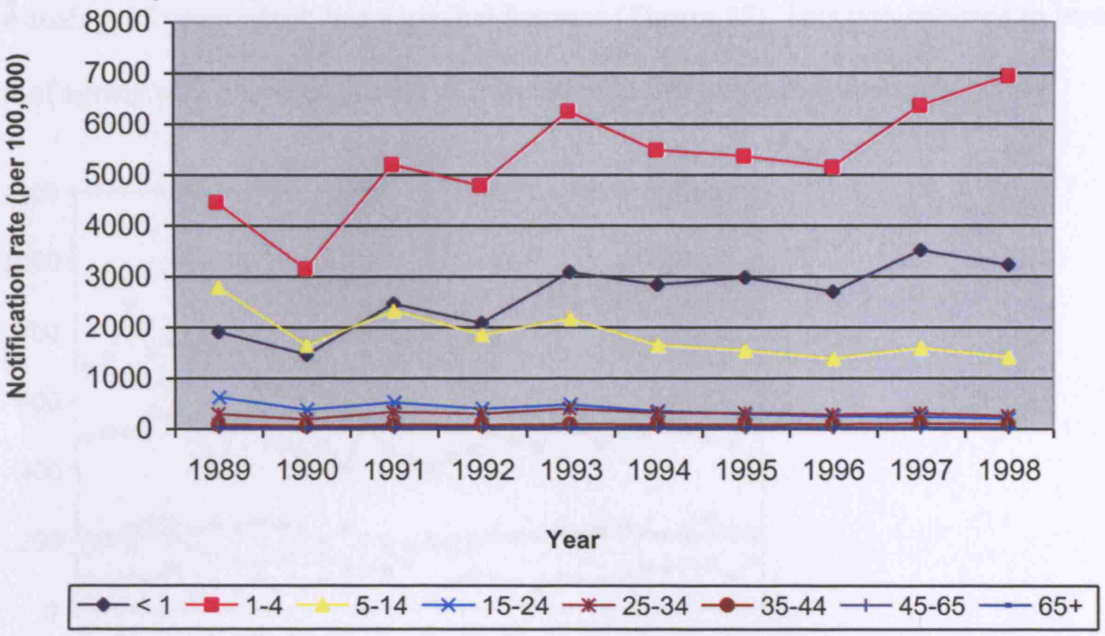


Figure 14: Age- specific notification rate (per 100,000 population) of varicella in Scotland, 1989-1998.(28)

Zoster

From studies of Miller et al, Chapman et al, and Lowe et al, average annual incidence (all ages or age-standardised) of zoster remained relatively stable in 1967-2001 in England and Wales (see **Figure 11** on page 46 for changes reported by Lowe et al).(16;39;73) Brisson et al reported a slight rise in overall incidence since the beginning of 1980s.(40) Average incidence rate increased from 310 per 100,000 person-years to 380 per 100,000 person-years in about 20 years (1979-1997). This rise came mainly from those $\geq$ 65 years. However, this change was not significant and the overall proportion of cases in each age group remained relatively stable over time. In another study by Brisson et al, the authors reported gradual increase in overall incidence rate over the 1990s due to ageing.(20) Changes in zoster epidemiology was best demonstrated Fleming et al who had an analysis of zoster data from 1970 to 2001.(42) In this

32-year study period, incidence rate of zoster was consistent in all age groups except in individuals ≥ 65 years which had a gradual increase (**Figure 15**). This was believed to be as a result of ageing with observed growth of population in this group over the study period.

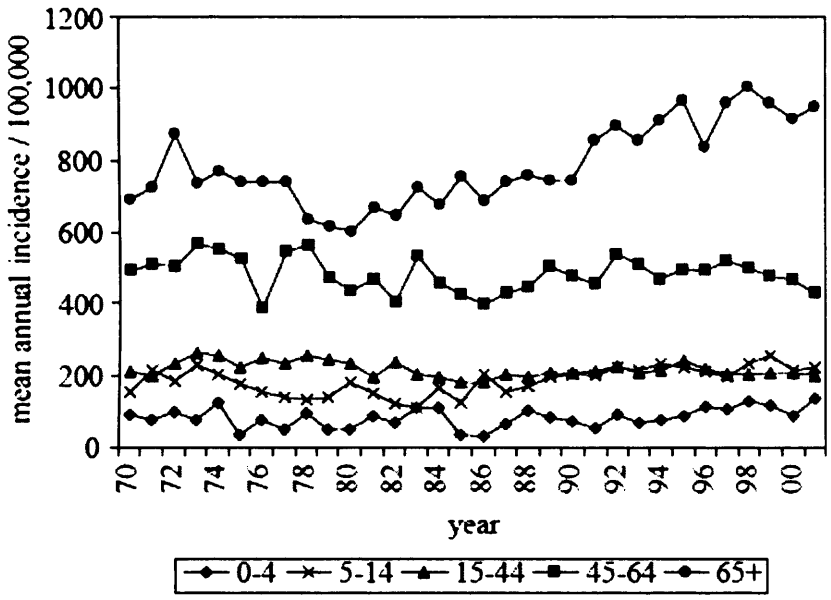


Figure 15: Annual incidence of zoster in England and Wales by age, 1970-2001.
Copied from Fleming et al, 2004.(42)

Varicella Sero-prevalence in the UK

Seropositivity gives evidence of previous infections as measured by presence of VZV specific IgG. WHO stated that VZV infection was experienced by almost every individual by early adulthood.(9) This was supported by expert groups in US and Canada.(44;75) In Europe, over 90% individuals in Western Europe (UK, France, Germany, Switzerland, Spain, and Czechoslovakia) acquire immunity to VZV before reaching adulthood.(76-78) A UK study by Vyse et al reported 53% children aged 5 years were seropositive for VZV.(79) This rose to around 85% in those aged 15-20 years. Kudesia et al found that in those 20-39 years of age, over 90% were seropositive for varicella.(74)

Key Messages

- VZV infection is an important public health issue in UK. Overall, incidence of varicella decreased with age while that of zoster increased with age. Disease burden was greater with zoster than with varicella in terms of morbidity and mortality.

- In England, Wales, and Scotland, crude annual incidence rate of varicella was about 350-650 per 100,000 population in the past 10 years (since 1996). In Northern Ireland, the estimated incidence rate was lower, at about 200-400 per 100,000 population, except the year 1992 (610 per 100,000 population).

- Two epidemics of varicella had been reported in England and Wales in the period 1967-1985, one in 1967 and another in 1980.

- Half the UK children acquire varicella by age 5 and 85% are infected before reaching adulthood.

- Lifetime risk of developing zoster was about 23-30%. Around 10% and 25% UK individuals younger than and older than 45 years suffered from at least one attack of zoster respectively. Average incidence was around 400-500 per 100,000 population. Zoster related morbidity and mortality increase sharply with increasing age. About 15% of those suffer from zoster would have PHN.

- For every 100,000 UK population who acquire VZV infection, about 4-9 will die from the primary infection and 25 will die from zoster. The probability of death increases with increasing age. 40-80% and nearly 100% of who die from varicella and zoster respectively are adults $\geq$ 15 years. There are 12-20 and 33-63 died of varicella and zoster respectively in 1999-2004.

- For varicella, there was an upward shift to adults before the 1980s but proportion in this group started to decline since mid-1980. In children, a shift of varicella from 5-14 years to 0-4 years was seen at the same time. Incidence in zoster was relatively stable in all age groups over time except in those $\geq$ 65 years which had a gradual rise over the past 3 decades.

2 Economic Consideration

Cost effectiveness analysis is important in UK as vaccines included in the routine childhood vaccination programme are provided free by the National Health Services (NHS). Resources of NHS, like many other countries, are limited. The following is an evaluation of the economical impact of VZV infections currently in UK. As zoster related death is rare but its effects on health associated quality of life can be severe, some studies also included the Quality-Adjusted Life-Years (QALYs)(A measure that combines mortality and quality of life gains, outcome of a treatment measured as the number of years of life saved with adjustment for quality).(80)

Scott et al carried out a prospective observational study conducted in 18 GP practices in East London over 8 months reported that an average cost secondary to zoster was £1,048 per year.(81) Medical costs were highest in those aged over 65 and societal costs (days of work lost) highest in those aged under 65 years.

Brisson et al used mathematical model to calculate direct (GP consultations, hospitalizations, and prophylaxis immunoglobulin prescription) and social costs (direct medical costs, plus work loss and household expenditures) for varicella related diseases.(82) It was estimated that direct medical cost was £35 million per year. Zoster accounted for 63% (£ 22 million) and varicella 37% (£13 million). Overall social costs was £223 million annually, 76% (£169 million) was due to zoster. QALYs lost for both varicella and zoster was 18,000 (range 14,000-29,000) per year in 1993-2000. 80% was due to zoster.

Edmunds et al estimated financial lost due to zoster and PHN using epidemiological data over long term (1947-1972 and 1991-1992) in England and Wales. Nearly £47.6 million (range £34-£74 million) was spent on these conditions each year.(41) Of this, 68% (£32.6 million) was due to acute zoster and 32% (£15 million) was due to PHN. Costs included GP consultations, hospitalizations, and prescription of antiviral drugs (acyclovir, famciclovir, and valaciclovir). The QALYs lost was around 20,000 per year in England and Wales in 1995-1999. 87% was due to PHN.

Davis et al published a study in 1994 to estimate costs of NHS in treating PHN in the UK.(83) It reported that based on a 1-year incidence cohort of 21,000-78,200 cases of PHN, the lifetime costs was £4.8-17.9 million per year.

Key Messages

- Varicella related diseases are important economic burden to UK.
- Overall costs are £35-223 million per year depends on the definitions.
- QALYs lost is 18,000-20,000 per years.
- 60-80% of this burden is associated with zoster and related complications.

3 Alternative Strategies

Apart from routine childhood immunisation, there are several other alternatives strategies to control varicella infection. These include vaccination of susceptible children, adolescents or adults, post-exposure prophylaxis with varicella zoster immunoglobulin (VZIG), and anti-viral therapies.

As half UK children will be infected by age 5 and 85% will acquire the disease by adolescence, immunisation of susceptible adolescents and adults will be at an individual level which is unlikely to eliminate VZV infection. The only feasible way to achieve elimination is mass immunisation of children at a population level. WHO suggested that the optimal age for varicella immunisation was 12-24 months of age.(9)

Post exposure Prophylaxis

VZIV can reduce the risk of developing clinical varicella if given within 10 days of exposure. As availability of suitable donors of VZIG is limited and its supply in UK is scarce recently, it is recommended in high risk groups only. It is not recommended as routine prophylaxis after exposure in healthy children or adults.(3;84) High risk groups include neonates, pregnant women, and immunocompromised individuals.

Drug Treatment

Varicella is usually a self-limiting disease in children. Symptomatic treatments with, for example antipyretic, antihistamine, and calamine lotion, are recommended. In adults without complication and the disease is not severe, treatment aim is still to relieve symptoms. Antiviral drugs such as acyclovir might be indicated in high risk groups.(49;85) These drugs are, however, not recommended for healthy adults and children without complication.(85) A review found that acyclovir was effective in reducing the number of days with fever and the maximum number of skin lesions in healthy children. However, its clinical importance in healthy children remains uncertain.(86) Another review also questioned the clinical importance of antiviral drug in healthy individuals.(87)

Key Messages

- VZIG and antiviral drugs are not a good choice for controlling VZV infection. Immunisation will be the only strategy to reduce the disease burden.

- Immunisation of susceptible adolescents and adults is at an individual level and will not lead to disease elimination.

- Mass immunisation of children at a population level would be the only strategy which could result in elimination of disease.

- WHO recommended that the optimal age for varicella vaccination was 12-24 months of age.

4 Vaccine Issues

Vaccine issues, including safety and efficacy, are fundamental questions affecting whether a new vaccine is worth adding to the national immunisation programme. Routine vaccination is a preventive measure to offer vaccines to individuals, mostly healthy children. The tolerance to adverse events thus should be lower than in the case of administrating therapeutic agents to individuals who already affected from a condition.

Development of Varicella Vaccine

All currently licensed varicella vaccines were derived from the Oka strain of VZV. This strain was isolated from the vesicle of a 3-year-old healthy Japanese child (with the family name Oka) with natural varicella in 1974 in Japan by Takahashi. The virus was attenuated through sequential propagation in cultures of human embryonic lung cells, embryonic guinea-pig cells and finally human diploid cells (WI-38 and MRC-5) for several times.(88;89) Different commercial strains have varying degree of attenuation.(90)

Target Population

According to WHO, target of the varicella vaccine immunisation could be infants, or non-immune adolescents and adults. For routine immunisation in infants, the optimal age recommended was 12-24 months.(9)

Vaccine Type

The only vaccines that are currently recommended by WHO for vaccination were all derived from the live attenuated Oka strain vaccine.(7)

Current Status of Use

Varicella vaccine was first licensed for use in high risk children in Europe in 1984, in Japan in 1986. Licensure was extended to healthy children in Japan in 1986, in Korea in 1988, in US, Germany and Sweden in 1995, and Canada in 1998.(91)

According to WHO, varicella vaccination is currently included in the national childhood immunisation programme of 10 countries to date (see following charts).(92) Germany is the only European country with routine childhood immunisation against VZV. This programme was incorporated into the routine immunisation schedule in July 2004.(93) Canada added varicella vaccine to the routine childhood schedule since 2004 (to all children 12 months of age)(94) but is not currently on the list of WHO. According to the Public Health Agency of Canada, varicella vaccine is now on the routine schedule of all Canadian provinces except Yukon Territory.(95) Australia just commenced a national programme in November 2005.(96)

Europe

Country	Schedule
Cyprus*	13-18 months
Germany**	11-14 months
Switzerland^	11-15 years

* In public sector it is given to high risk groups while in private sector it is given universally

**Also given to adolescents without history of varicella and specific high risk groups

^ Adolescents without history of varicella only

West Pacific

Country	Schedule
Australia	18 months 10-13 years*
Republic of Korea	12-15 months

* As catch-up programme

America

Country	Schedule
Brazil*	≥ 12 months
Canada#	12 months
Dominican Republic**	12 months
Uruguay	12 months
US##	12-18 months

* And also special groups

** Part of country only

Not on WHO list. Information from Public Health Agency of Canada.(95)

And adolescents without history of varicella

Eastern Mediterranean

Country	Schedule
Qatar	12 months

Varicella vaccines are offered to high risk groups in the following 8 countries.(92)

Europe

Country	Comment
Italy	high risk groups
Slovenia	risk groups
Spain	High risk groups
United Kingdom	Non-immune health care workers

America

Country	Comment
Costa Rica	Risk groups 15 months to under 14 years
Mexico	Immunocompromised children

Eastern Mediterranean

Country	Comment
Kingdom of Bahrain	High risk groups
United Arab Emirates	Risk groups

Remarks: These data were provided through WHO-UNICEF Joint Reporting Form and WHO regional offices. The terms "high risk groups or "risk groups" were not defined except in the cases of UK and Mexico.

Varicella Vaccine in UK

Despite the use of varicella vaccines in healthy children in Asia, they were not considered candidates in the Western world initially.(97) The concern was the duration of protection the vaccine could provide as if immunity waned with time there was a possibility of shifting the disease burden to susceptible adults who had greater risk of developing complications and deaths. In UK, some early trials of vaccine efficacy and safety started in early 1980s.(98) There are currently two varicella vaccines licensed in UK. The first one, Oka/RIT (marketed as Varilrix, GlaxoSmithKline) was launched in July, 2002.(99) Another one, Oka/Merck (marketed as Varivax, Sanofi Pasteur MSD), was licensed in 2004.(100) **Table 31** is a comparison of the basic information about these two vaccines.

	Varivax (Oka/Merck)	**Varilrix (Oka/RIT)**
UK manufacturer	Sanofi Pasteur MSD	GlaxoSmithKline (GSK)
Date licensed in UK	2004	2002
Virus strain	Oka/ Merck strain Had undergone 31 serial passages in cell culture	Oka/ RIT strain Had undergone 35 serial passages in cell culture
Minimum potency level	1350 pfu	1995 pfu
Shelf life when stored at +2 C to +8C	18 months	24 months
Life time after reconstruction	30 minutes	90 minutes
Price in UK	£32.14	£29.37
Licensure in UK	To individuals ≥ 12 months	To individuals ≥ 12 months

Table 31: Comparison of Oka/ Merck (Varivax) and Oka/ RIT (Varilrix).

Source: NACI(75), Lau et al(90), DH.(100), Sanofi Pasteur MSD(101;102), and GSK.(103)

Studies on Varicella Vaccines

This part includes reviews by international expert groups, key papers, and clinical trials and meta-analysis from PubMed. Japanese studies were included here as well as the Japanese had the longest clinical experience (30 years) in varicella vaccination. Brief summaries of these studies can be found in **Appendix D**.

Background information

United States

Currently 3 vaccines against VZV are licensed in US.(104) Varivax (Oka/Merck) was the only one licensed before 2005. A combination vaccine, ProQuad (MMRV, for individuals 12 months to 12 years of age) and Zostavax (for individuals $\geq$ 60 years) were licensed in 2005 and 2006 respectively.(105) US studies before 2005 were all based on Oka/ Merck vaccine.

Canada

2 varicella vaccines are currently licensed in Canada. Oka/ GSK was licensed in 1999 and Oka/Merck was licensed in 2002.(75)

Japan

It is not clear which vaccine(s) is/are licensed in Japan.

4.1 Vaccine safety

Safety on varicella vaccine included in this thesis focused mainly on post-licensing studies as rare adverse events previously not detected before licensure were apparent with increasing use after mass immunisation. US post-licensing vaccine studies were based on two main post-licensing surveillance systems, the national Vaccine Event Reporting System (VAERS) and Merck's Worldwide Adverse Experience System (WAES). Details on the data sources of these systems can be found in **Appendix E**. Definitions of adverse events can be found in **Appendix F**.

i) Frequent Events

From passive surveillance data, 95% reported cases were non-serious. Minor events such as injection site discomfort (including pain, swelling, and haematoma), fever, mild generalised varicella like rash, and rash at injection site occurred in 19%, 15%, 5% and 3% individuals respectively. Less than 0.01% had febrile convulsions. Serious complications such as encephalitis, ataxia and thrombocytopenia had been reported in US, but at lower rates than following natural infections. Casual relationship could not be determined in most cases because of insufficient data. Number of reported adverse events declined continually over years since implementation of national immunisation.(44;106;107)

In the first 3 years (1995-1998) following mass vaccination, overall adverse events occurred at a rate of 67.5 per 100,000 doses.(108) 4% (3 per 100,000 doses) were serious events, including 14 deaths (**Table 32**). Death, other serious events, and non-serious events occurred at rates of 0.1, 2.8, and 64.5 per 100,000 doses respectively.

Age (years)	Deaths	Other serious events	Non-serious events	Total
< 1	0	6	37	**43**
1- <2	6	119	1,250	**1,375**
2-4	3	51	1,486	**1,540**
5-9	1	25	1,016	**1,042**
10-17	1	9	310	**20**
>17	3	46	1,365	**1,414**
Unknown	0	15	825	**840**
Total (%)	**14 (0.2%)**	**271 (4.1%)**	**6,289 (95.7%)**	**6,574 (100%)**

Table 32: Adverse events reported to VAERS following immunisation with Oka/Merck (Varivax) vaccine in US, 1995-1998. Source: Wise et al.(108) (Total cases reported = 6,574)

In the first 4 years after licensure (1995-1999), average adverse rate decreased to 50 per 100,000 doses distributed (**Table 33**).(109)

Study year	Reporting rate (per 100,000 doses)
1995- 1996	66
1996- 1997	55
1997- 1998	51
1998-1999	49
Overall	50

Table 33: Reporting rate of adverse events following vaccination with Oka/ Merck (Varivax) vaccine in US, 1995-1999.(109)

No serious adverse reactions had been reported in randomised controlled or uncontrolled trials.(110;111) 7-30% children developed mild and well tolerable local reactions. There was no increase in fever (0-36% depending on definition) or varicella like rash (5%) after vaccination over placebo in children. Adverse reactions did not increase with increasing potency (in terms of plaque forming unit, pfu) of vaccines.(110) Second dose of vaccine caused less reaction than the first. Minor event such as fever and injection site rash were seen in 15% and 4% after first dose of vaccine respectively. These were decreased to 11% and 2% respectively after second dose.(111)

ii) Uncommon Events

Ataxia, erythema multiforme/ Steven Johnson syndrome, encephalitis/ meningitis/ hemiparesis, thrombocytopenia, and anaphylaxis were seen at 0.15, 0.14, 0.11, 0.09, and 0.04 per 100,000 doses distributed respectively.(109) **Table 34** is a comparison of adverse events reported following varicella vaccination and other vaccines currently included in the routine immunisation programme of UK.

	Fever	Local reaction	Rash	Convulsion	Anaphylaxis	Thrombo-cytopenia
Varicella	10-15%	19-20%	4-6%	0.01-0.1%	Very rare*	0.2%##
BCG	-	90-95%	-	-	Very rare**	-
DTaP	10-25%	10-25%	-	0.007%	Very rare#	-
Hepatitis B	1-7%	5-9%	-	-	-	-
Hib	2-10%	5-25%	-	-	Very rare	-
MMR	5-17%	10%	5%	0.03%	Very rare#	0.003%
Pneumococcal	33%	25%	-	-	-	-

Table 34: Comparison of adverse events reported in different vaccines.

Source: Findings from above reviews and studies, and extra data from WHO and US CDC.(112;113)

* < 0.5 in 1 million doses ** < 1 in 6-900,000 doses

< 1 in 1 million doses ## result from one single study

4.2 Seroconversion and Vaccine Efficacy

Seroconversion rate was defined as the percentage of individuals who previously tested seronegative (VZV antibody negative) and were converted to be seropositive (VZV antibody positive and was above a defined level) at 6-8 weeks after vaccination. VZV antibody levels higher than a desirable level at these periods were found to be associated with reduced risk of developing breakthrough varicella.(114;115) VZV antibody level at 6-8 weeks was thus

regarded as a marker to correlate with vaccine effectiveness in preventing subsequent varicella

Seroconversion rate was 94-98% after one injection of vaccine in healthy children.(9;44;111;116) From the Japanese experience, immunity lasted for at least 10-20 years. From the US experience, VZV antibody was still detectable in 90-100% vaccinees (44;117) and provided 70-90% and 85-95% protection against any severity and severe diseases respectively in children after at least 6-10 years.(9;44;110;118) Some studies reported that with a second injection, both seroconversion rate and efficacy against disease of any severity increased significantly from 98% to 99.9% ($P<0.001$) and 94% to 98% ($P< 0.001$) respectively.(111;117) Other study reported no additional protection after more than one injection in children.(110). Similar efficacy had been demonstrated in both Oka/Merck (Varivax) and Oka/RIT (Varilrix) in one study.(75) Though study reported that vaccine efficacy was dependant on vaccine potency,(119) no difference in efficacy was detected in vaccines containing 1260-3625 pfu/ dose.(110) However, antibody response after varicella vaccination was found to be 10 times less than following natural infection in a review.(75)

4.3 Breakthrough Disease

CDC defined breakthrough disease as in vaccinated persons who develop varicella more than 42 days after vaccination.(120) Some outbreak studies in US will be included here.

From US post-licensing studies, breakthrough diseases occurred at a rate of 10-13 per 100,000 doses(108;109). Study with mathematical model predicted that full protection was

lost at a rate of 3% per year.(121) Statistically less vaccinated children acquired varicella than unvaccinated children in a short term (9-month) study (P<10(-9)).(116) Attack rate of breakthrough diseases in vaccinated children and placebo controls were 0-3% and 7-11% each year respectively.(110) Breakthrough diseases were milder than natural infections with most individuals had <50 lesions.(9;44;109;117;122) Risk of breakthrough infection was found to be increase with longer time from vaccination (≥ 3 years) and low antibody level 6 weeks after vaccination. Infectivity of vaccinees depended on number of skin lesions. With < 50 lesions, risk to infect others in household contact was half that of non-vaccinees. With > 50 lesions, the risk was the same.(75) One injection resulted in significant reduction in disease severity while one additional injection significantly increased efficacy and decreased breakthrough illness.(117)

In Japan, breakthrough rates varied between 2-20% up to 20 years' follow-up. Breakthrough diseases were milder with fewer skin lesions and shorter clinical course than the natural infection. Majority of cases had less than 50 lesions. Breakthrough illness was found to associated with lower post-vaccination antibody titre at 6 weeks after vaccination.(118;123;124) **Table 35** showed the breakthrough diseases reported in a 10-year follow-up in Japan. 75% cases occurred in the first 4 years after vaccination.

Time since vaccination (year)	Cases of breakthrough varicella (%)
1	19 (16%)
2	30 (25.2%)
3	25 (21%)
4	16 (13.4%)
5	8 (6.7%)
6	5 (4.2%)
10	12 (10.1%)
Total	**119**

Table 35: Number of breakthrough varicella following vaccination. Source: Ozaki et al (124)

Remarks: 3.4% individuals with unknown onset time of breakthrough diseases.

Outbreak Studies

Outbreaks were reported in US following introduction of vaccine programme from time to time. Attack rates were estimated to be 12-25% and 43-77% in vaccinated and unvaccinated individuals respectively. Vaccine efficacy was reported to be 56-89%, 90-99% and 100% against any severity, moderate to severe, and severe diseases respectively.(125-131) Breakthrough diseases were significantly milder with fewer cases with fever, shorter duration of rash, and miss fewer days from school.(125;126;129) These studies suggested that breakthrough diseases in vaccinated individuals could be contagious. Outbreaks lasted from 7 weeks to 3 months.

Risks of developing breakthrough disease were suggested to be associated with the following factors;

1) Length of time since vaccination (with duration $\geq$ 4-5 years since vaccination associated with 3-7 times higher risk).(126;130;131) Some studies reported no association.(129)
2) Age at vaccination (with vaccination at $\geq$12 and <16 months of age associated with 2-3 times higher risk).(130;132) Some studies again reported no association.(126;129)

Severity of diseases in these outbreak studies was defined as;

- Mild when there were < 50 lesions
- Moderate when there were 50-500 lesions
- Severe when there were > 500 lesion or disease of any severity that resulted in complications or hospitalisations

4.4 Risk of Herpes Zoster

Review studies reported that zoster had been reported occasionally in vaccinees and it might be possible that vaccine strain VZV had the ability to reactivate later in life.(9;110) This topic will be explored more under the section "Impact on epidemiology".

In US, post-licensing data did not show any significant increase in zoster in adolescents or adults after up to 11 years of mass immunisation.(75;133) In the first 3-4 years following mass vaccination, zoster developed at a rate of 1.3-2.6 per 100,000 doses in vaccinees.(108;109) There was evidence suggesting that zoster following vaccines did occur

but were at a rate lower than those following natural infections. Incidence rate was estimated to be 21 per 100,000 person-years, compared to 77 per 100,000 person-years following natural infections in children. 14 per 100,000 vaccinees developed zoster over 9 years following Oka/ Merck vaccination in US, compared to 42 per 100,000 population and 20 per 100,000 population in unvaccinated children of all ages and children under 5 years respectively.(110)

In Japan, some studies reported no subject developed zoster in 6-year (8429 subjects) and 20-year follow up (sample size not clear)(118;123) while other reported 0.7% (4 out of 571 vaccinees) individuals developed zoster in 10 years.(124)

4.5 Transmission of Vaccine Virus/ Secondary Transmission

There is concern that there is a risk of secondary transmission of the vaccine virus from vaccinees to their contacts.

From study of post-licensing surveillance in US, secondary transmission was estimated to occur at 0.57 per 100,000 doses at 1.5-8 weeks after immunisation.(109) Secondary transmission of vaccine virus did occur but was believed to be rare and limited to individuals with rash.(108) Some experts had different opinions and concluded that current data provided no firm evidence that there was secondary transmission from healthy vaccinees.(110;133) However, subclinical cases could not be excluded as seroconversion had been documented in un-vaccinated siblings of vaccinees without developing clinical varicella.(110)

Varilrix

Varilrix was licensed in a few European countries and India by 1998 and by Hong Kong and Brazil by 2001.(134) It is currently licensed in over 80 countries including UK and Canada but not US.(75;135) Most published studies were related to Oka/Merck vaccine. Studies on Varilrix came mainly from Asian/Pacific areas.(90) It had been assumed that Varilrix had comparable characteristics with Varivax as they derived from the same parental Oka strain VZV.(75) As this vaccine is also licensed in UK. Additional information about it is included here for reference.

In a case control study with about 500 healthy children aged 1-5 years (median 3 years) in Israel, vaccine efficacy was 88% and 100% against any severity and moderate/ severe diseases respectively.(136) Vaccination rates were significantly different, with 6.6% in cases (children contracted varicella) and 38.3% in controls (matched children without varicella) ($P<0.001$). Vaccinated children had significantly milder symptoms of breakthrough disease than unvaccinated children. They were less likely to have fever ($P<0.02$), missed less days from day care ($P<0.0004$), and their skin lesions dried faster (5 days versus 9 days, $P<0.02$).

In a retrospective study using database that included 25% of the population in Israel, children younger than 10 years who had received varicella vaccine were recruited to determine breakthrough rate and vaccine efficacy following immunisation. Efficacy was reported to be 92% in preventing clinical disease.(137)

A RCT study comparing high potent (16,000-50,000 pfu/dose) Oka/Merck and Oka/RIT in over 600 healthy 12-20 months (median 13 months) children in Hong Kong showed that both vaccines were well tolerated.(90) No vaccine-related serious reaction was reported in either vaccine. Efficacies were similar. Immunogenicity however, varied with the vaccine and dose used. Oka/Merck was more immunogenic than Oka/TIR. 97%, 95% and 86% achieved protective antibody level at 6 weeks post vaccination in healthy children receiving Varivax 50,000 pfu, Varivax 16,000 pfu, and Varilrix 40,000 pfu respectively. Clinical significant of these was not clear as the efficacies were similar. The author proposed that this might be due to the fact that Oka/TIR went through more passages in cell culture and thus were more attenuated than the Oka/ Merck.

Combination Vaccines

Combining vaccines together can reduce the number of injections and thus enhances compliance and coverage rate. A combination vaccine, ProQuad, was already licensed in US in 2005 for use in children aged 12 months to 12 years.(138) Early studies with combination of varicella vaccine and MMR vaccine were rather disappointing. Results showed that the measles component interfered with the varicella component when the four vaccines were combined into one. Although seroconversion rates with the MMR components were similar to those achieved when it was given alone, the immunogenicity of varicella vaccine was reduced with lower VZV antibody level following administration of combination vaccine.(139-141)

After years of research, study showed that protective VZV antibody response could be achieved by increasing the VZV potency in the MMRV vaccine. In a study with 1,559 children aged 12-24 months, one injection of these highly potent combination vaccines

resulted in comparable antibody responses to the 4 vaccine components to that achieved after simultaneous administration of MMR and varicella vaccine. Boosting of this antibody response was observed after a second dose.(142) The varicella vaccines used in this study were of 3,019-17,738 pfu/dose.

In a large scale multi-centre case control study in US and Canada with nearly 4,000 children aged 12-23 months in 2006(143), cases were given MMRV while controls received MMR and varicella vaccines concomitantly at different sites. Results showed that seroconversion rates to the four components were similar in cases and controls. Antibody maintenance rates were >95% for each of the component after one year and was also comparable in cases and controls. Adverse events within 42 days after vaccination were reported at similar rates in the two groups except fever (but not febrile convulsion), which was seen significantly more in cases than control (P=0.001). The varicella vaccines used in this study were 4.4-4.73 log10 pfu/dose.

A review study reported that adverse events following immunisation of combination MMRV vaccine was similar to that following vaccination of MMR vaccine or varicella vaccine alone.(133) MMRV had similar efficacy as when varicella vaccine and MMR were administered separately.(110)

Key Messages

- Varicella vaccines were generally well tolerated with adverse reactions occurred at a rate of 50-70 per 100,000 doses distributed. 95% were non-serious.

- Vaccine efficacy was 70-90% and 85-95% against any severity and severe diseases respectively 6-10 years after vaccination (except in outbreak cases where rate as low as 56% was documented).

- From US experience, breakthrough varicella occurred at a rate of 10-13 per 100,000 doses. Full protection lost at 3% per year. From Japanese experience, breakthrough attacks occurred at 2-20% up to 20 years. From studies in both countries, breakthrough diseases were milder than natural infections with less skin lesions, fewer cases with fever, and shorter clinical course.

- Incidence of zoster in vaccinees varied from study to study but was reported be either no more than or even less frequent than following natural infection.

- Whether length of time since vaccination and age at vaccination will affect vaccine efficacy was controversial.

- Second injection of vaccine generally associated with fewer adverse events than the first injection. However, whether a booster injection could provide additional protection was controversial.

- Oka/RIT (Varilrix) was also well tolerated. It was less immunogenic than Oka/Merck (Varivax) but the clinical importance of this was not clear as both vaccines had similar efficacy.

- Old generation combination vaccines were disappointing with reduced immunogenicity of varicella component. Early studies on newer generations were encouraging and might be the future hope.

5 Impact on Epidemiology

5.1 Theories

It was postulated that zoster occurred as a result of decreased immunity to VZV and exogenous exposure to varicella boosted this immunity and therefore reduced zoster in individuals with latent VZV infections.(144) This hypothesis was supported by studies which showed that adults living with children had more exposure to varicella (145) and that this exposure was protective against development of zoster.(146)

Following these hypotheses, mathematical model predicted that cases of zoster would significantly increase following mass infant immunisation because of reduction of exogenous booster (circulating VZV). This theory suggested that there would be an immediate decline in cases of varicella following mass vaccination. Susceptible individuals (unvaccinated and primary failures) gradually accumulated until a threshold was reached which resulted in epidemic.(147) Because of the decrease in varicella, exogenous booster was reduced leading to increase in cases of zoster. Thus the reduction in disease burden of varicella was offset by an increase in burden of zoster. The more the reduction in incidence of varicella the more increase in cases of zoster. Incidence of zoster would decrease in the long term provided that vaccine virus reactivated at lower rate than the wild type virus and seroconverted individuals did not develop zoster. However, this benefit was not expected to occur at least in the first 40-60 years following mass immunisation. Catch up programmes offered to older non-immune individuals could avoid the epidemic and reduced mortality but this had no effect on long term epidemiology.

5.2 Real Examples

This section will focus on two countries, the US and Japan, the two countries with longest history of licensed varicella vaccine.

5.2.1 US Experience

Background

In 1972, primary varicella became nationally notifiable in the US. However, it was removed from the list of national notifiable disease since 1991.(44) Only some states continued to report cases to US Centers of Disease Control and Prevention (CDC) since then. In order to improve surveillance on mortality, varicella was designated as a nationally notifiable disease again in 2002.(148) Zoster is not a notifiable disease in US. Varicella related deaths became nationally notifiable in January, 1999.(149)

Oka/Merck was licensed in US in March 1995.(150) It was recommended for routine immunisation for 12-18 months of age and susceptible older children, adolescents and adults.(151) In February 1999, the US Advisory Committee on Immunization Practices (ACIP) suggested mandatory child care and school entry requirements.(152) In 1995, an active surveillance project, the Varicella Active Surveillance Project, was established in 3 areas in US, jointly by CDC and local health departments.(153) The 3 areas were: Antelope of Los Angeles (LA) County, Travis County of Texas, and West Philadelphia of Philadelphia. Despite encouragement to report all cases of varicella, each state had its own policy. In LA, varicella was not reportable at least in the period 1995-2000. In Texas, it was reportable since before 1995. In Philadelphia, it became reportable since 1995.

Impact on Varicella

Incidence

According to CDC, varicella was endemic in US in the pre-vaccination period.(44) As almost all individuals were expected to acquire varicella by adulthood, the number of cases was estimated to approximate the birth cohort at that time. Crude incidence rate was 100-180 per 100,000 population in 1980-1994.(154;155) The distribution of disease burden was rather similar to that in UK. 85% cases occurred in children < 15 years (**Table 36**). Incidence rate was highest in the 1-4 years and decreased with age (**Figure 17**). Cases after 20 years were uncommon.(44) Adults accounted for only 5% cases but 35% deaths. Case fatality rate, on the other hand, increased with increasing age except in neonates who were also high risk group (**Figure 18**).

Age (years)	Proportion (percentage)	
<1		
1-4	39%	
5-9	38%	85%
10-14		
15-20	8%	
≥ 20	7%	

Table 36: Proportion of cases of varicella by age in US, 1990-1994.

Source: US CDC.(44)

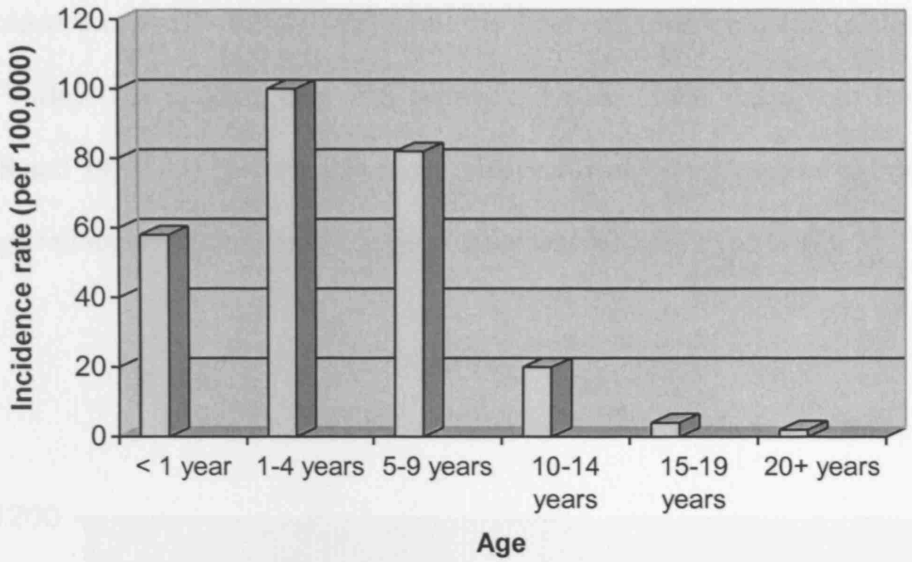


Figure 16: Incidence rate (per 100,000 population) of varicella in US by age, 1990- 1994.

Source: US CDC.(44)

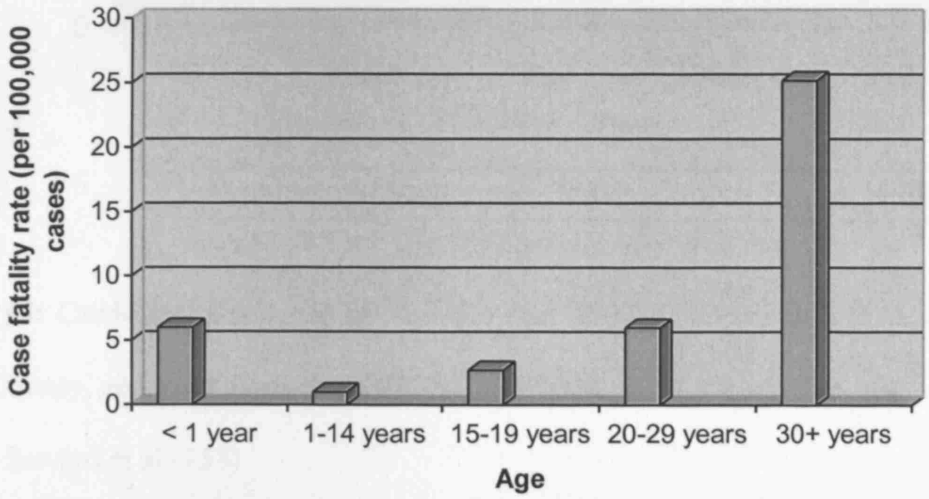


Figure 17: Varicella case fatality rate (per 100,000 cases) in healthy individuals in US, 1990-1994.

Source; US CDC.(44)

After introducing routine varicella immunisation, there was statistically significant decline in overall incidence rates (P= 0.002-0.02) in all the 3 surveillance areas and in all age groups in Antelope Valley (age specific data was available for this areas only, with P = 0.002-0.02) (**Figure 18** and **19**).(153) Decline was most remarkable among preschool children 1-4 years. The average reduction in number of reported cases was 70-85% (**Table 37**).

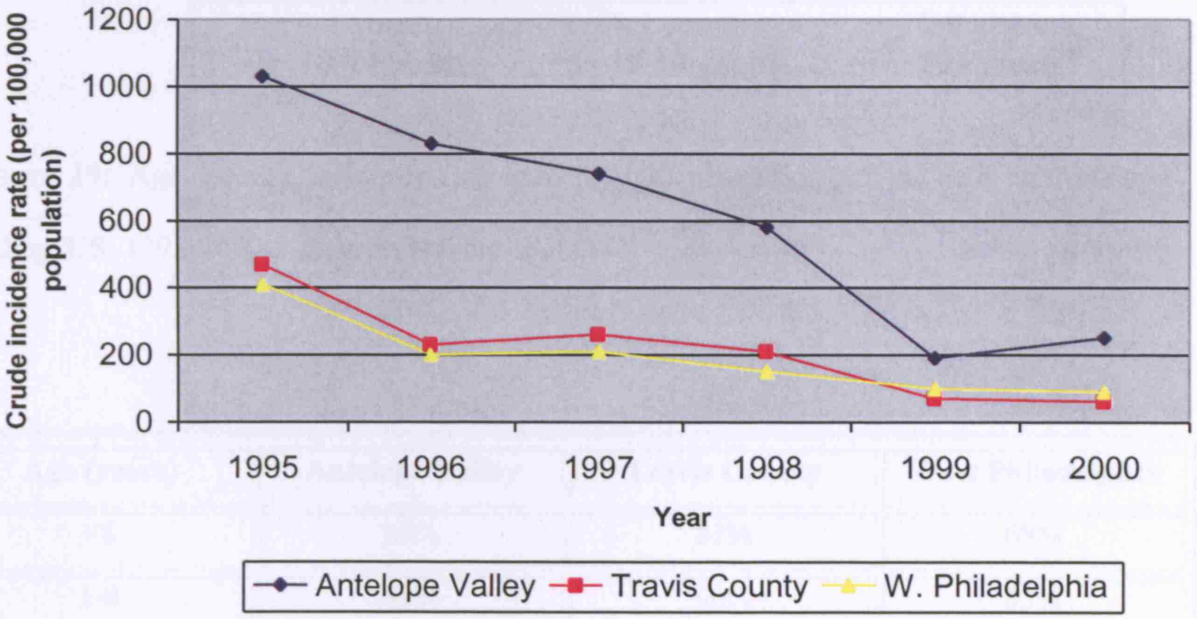


Figure 18: Crude incidence rate of varicella (per 100,000 population) in Antelope Valley, Travis County, and West Philadelphia, US, 1995-2000.

Source: Seward et al.(153)

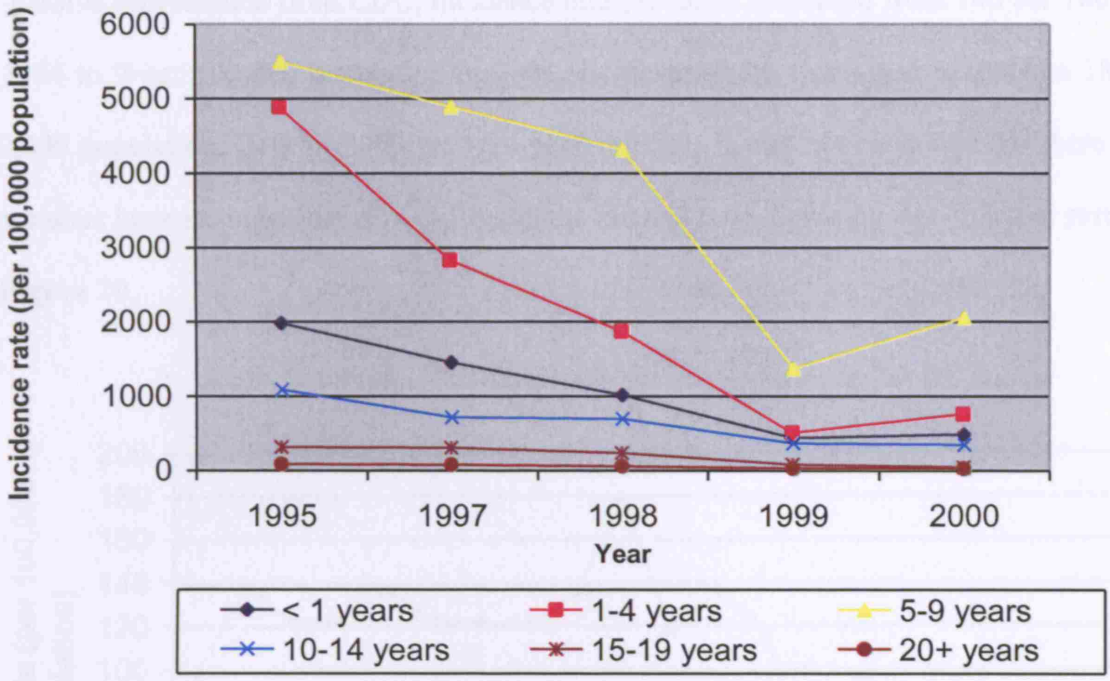


Figure 19: Age-specific incidence rate (per 100,000 population) of varicella in Antelope Valley, US, 1995-2000. Source: Seward et al.(153)

Age (years)	Antelope Valley	Travis County	West Philadelphia
<1	69%	81%	68%
1-4	83%	90%	83%
5-9	63%	77%	77%
10-14	65%	75%	80%
15-19	85%	83%	81%
20+	66%	64%	68%
Average	**71%**	**84%**	**79%**

Table 37: Proportion (percent) of reduction in reported varicella cases by 2000 (with respect to number of reported cases in 1995), US. Source: Seward et al.(153)

By passive surveillance from CDC, incidence rate (all ages) decreased from 140 per 100,000 in 1994 to 7 per 100,000 population in 2003. However, there was a rise in 2004 to 18 per 100,000 population. Data in 2005 was not yet available. It was not clear whether there was continuous increase in incidence. Combining the pre and post- licensing data together resulted in **Figure 20**.

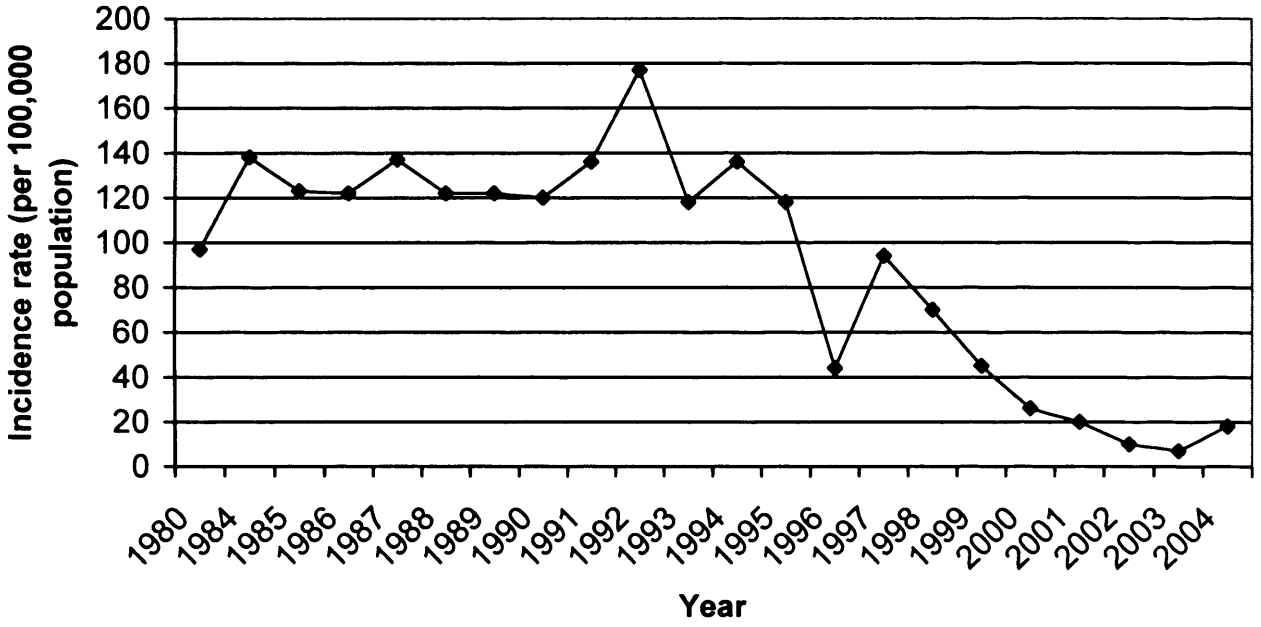


Figure 20: Crude incidence rate (per 100,000 population) in US, 1980- 2004.

Source: US CDC.(148;154;156;157)

Hospitalisation and Complications

When compared with data in pre-licensing period in 1988-1995, the only significant finding 4 years after licensure (1996-1999) was a decrease in mean length of hospital stay from 5.4 days to 4.0 days ($P<0.001$).(158) There was a trend decreased towards decrease in hospitalisation but this was not statistically significant. There was no shift in incidence of hospitalisation in any age group.

In another study, varicella related hospitalisation rate (population- adjusted) decreased over time from 1993 to 2001 in all age groups (**Figure 21**).(159) The most dramatic decline occurred in the age group 0-4 years. There was an associated reduction in proportion of all varicella related hospitalisations in this group 0-4 (**Table 38**). There was gradual increase in vaccine coverage rate in the 19-35 months children over time (**Figure 22**). Decrease in varicella disease burden was also demonstrated by reduction in hospital expenditure. While total annual varicella related hospitalisation expenditures (all diagnosis, standardised to 2001 US dollars) increased from USD 407 billion in 1993 to USD 549 billion in 2001, annual hospitalisation expenditures for varicella related hospitalisation decreased from USD 160 million to USD 66 million in the same period.

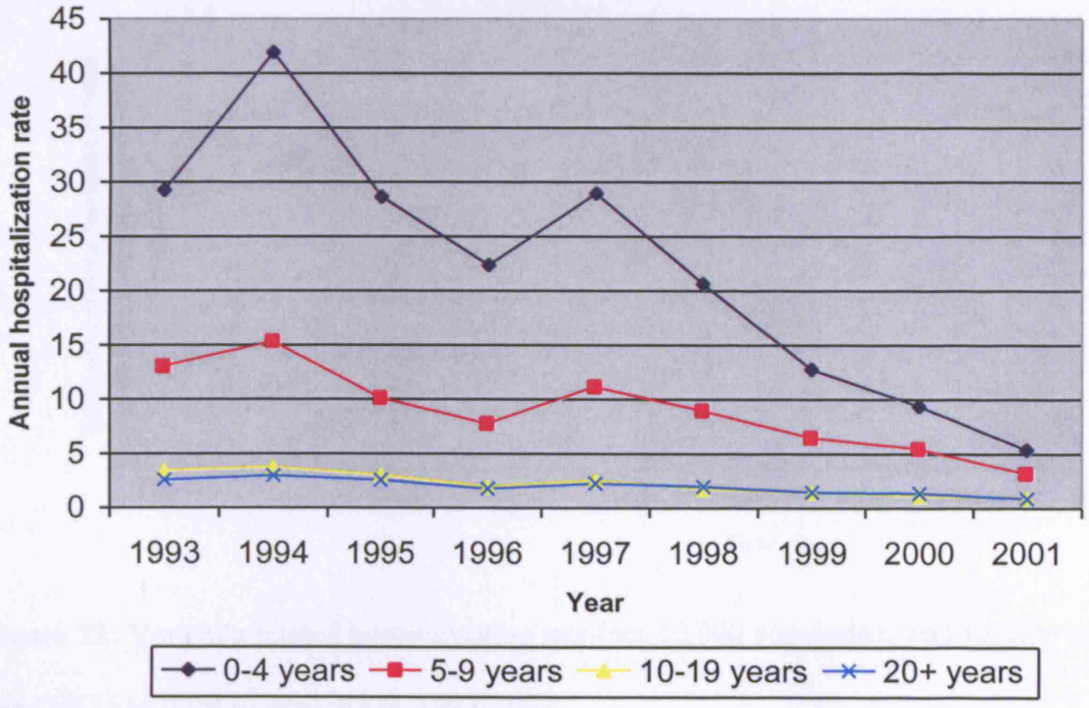


Figure 21: Population- adjusted varicella related hospitalisation rates (per 100,000 population) in US by age groups, 1993-2001.

Source: Davis et al.(159)

Year / Age (years)	1993	2001
0-4	41%	28%
5-19	26%	26%
≥ 20	33%	46%

Table 38: Proportion of varicella related hospitalisations in US by age groups, 1993 and 2001. Source: Davis et al.(159)

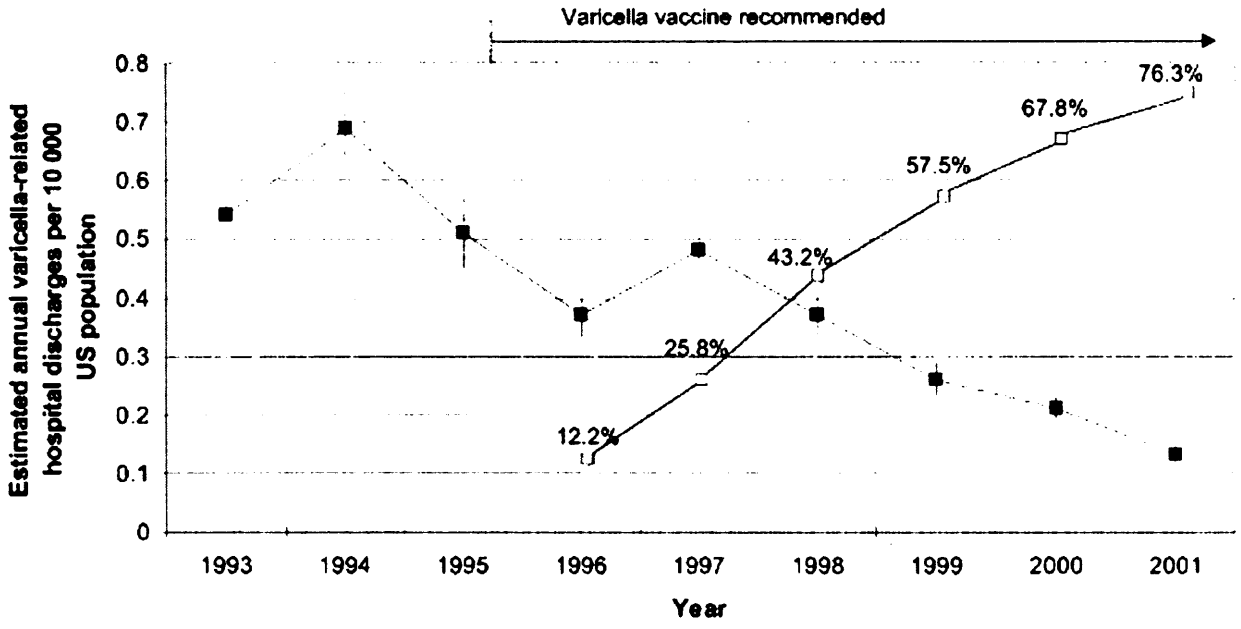


Figure 22: Varicella related hospitalisation rate (per 10,000 population) and vaccine coverage rate (19-35 months of age) in US, 1993-2001.

Source: Davis et al.(159)

Mortality

There were 47-138, 81-124, and 16-99 deaths per year in US in 1970-1980s, 1990-1995, and 1996-2003 respectively (**Figure 23**).(44) Absolute number of deaths gradually decreased after mass immunisation but the statistical significance of this decline was not sure.

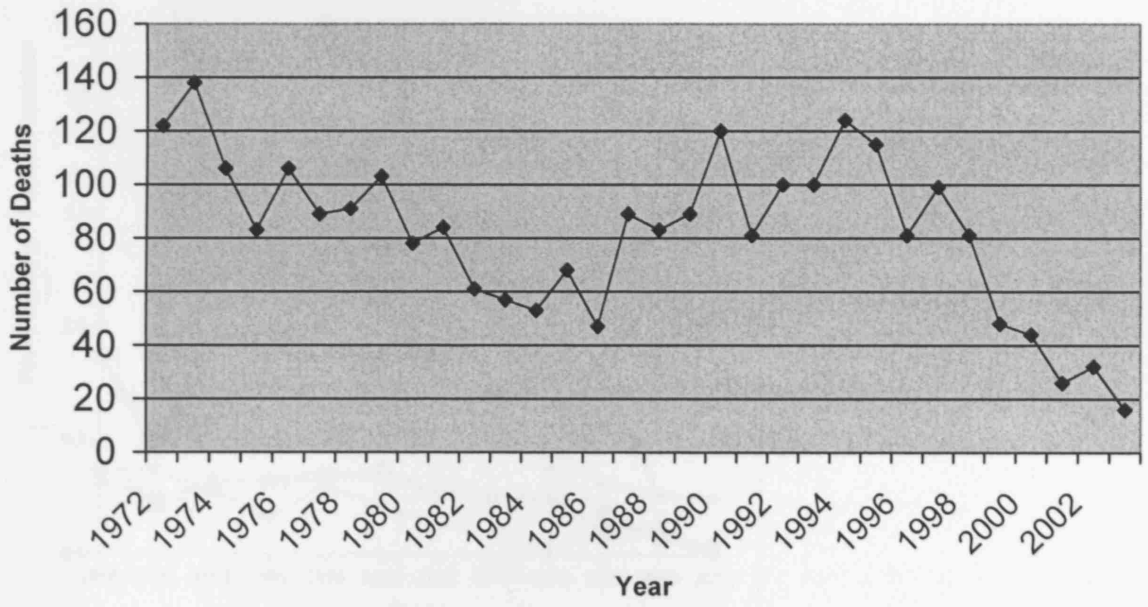


Figure 23: Deaths from varicella in US, 1972- 2003.

Source: CDC.(44)

In a mortality study comparing pre (1990-94) and post-licensing (1999-2001) data, there was a significant drop of the overall age-adjusted mortality rate (varicella as both an underlying and contributable cause) from 0.056 per 100,000 to 0.023 per 100,000 ($P < 0.001$).(160) This was equivalent to about 60% reduction. If counting only deaths due to varicella as an underlying cause, there was significant decrease in the death rates in all age groups ($P < 0.001$) except in neonates and individuals $\geq$ 50 years (**Figure 24**).

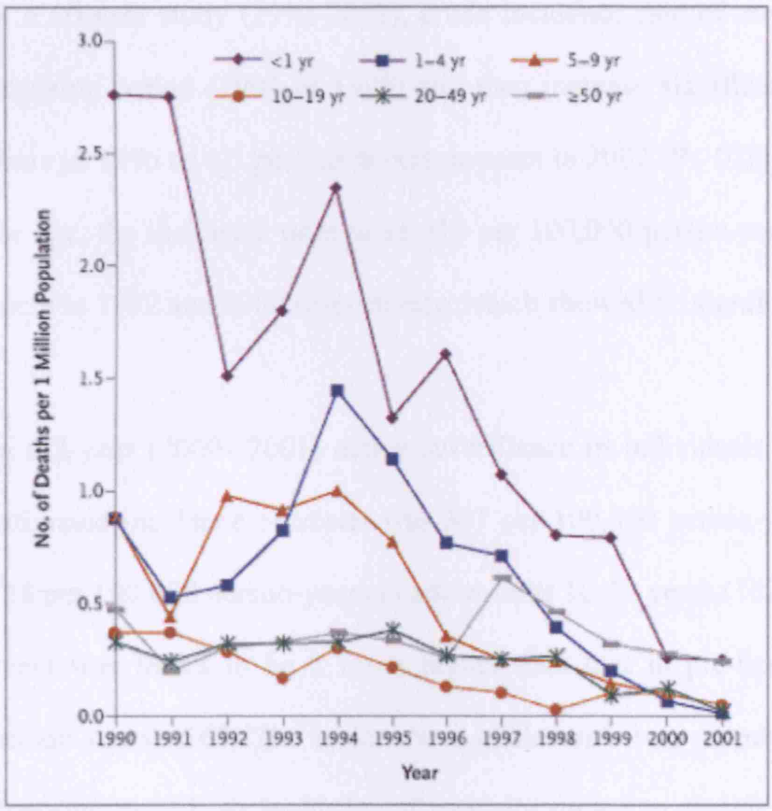


Figure 24: Age- specific annual mortality rate (per 1,000,000 population) of varicella as an underlying cause of death in US, 1990-2001.

Copied from Nguyen et al.(160)

Impact on Zoster

The effect on the incidence of zoster after introducing vaccination was less certain.

In a 10-year study (1992-2002), crude incidence rate of zoster fluctuated over time in pre-licensing period (1992 to 1995) and than increase significantly from 3.9 per 1,000 person-years in 1996 to 4.5 per 1,000 person-years in 2002 ($P< 0.001$).(161) However, after adjusted for age, the incidence rates were 410 per 100,000 person-years and 350 per 100,000 person-years in 1992 and 2000 respectively, which showed no significant difference.

In a 2-year (2000- 2001) active surveillance in individuals < 20 years in Antelope Valley, estimated incidence of zoster was 307 per 100,000 person-years in children < 10 years and 138 per 100,000 person-years in adolescents 10-19 years.(162) The incidence in children < 10 years was found to be 2 times higher than that in pre-licensing period (145 per 100,000 person-years).(163) The incidence in adolescents was reported to be the same as that in pre-licensing period. As incidence of varicella started to decline only 2-3 years before the study, the authors suggested that the observed difference in prevalence might be due to the fact that the adolescent cohort had prior boosting by circulating VZV.

Key Messages

- From both active and passive surveillances, the disease burden of varicella (incidence, hospitalisation, and mortality) declined after mass immunisation.

- The impact on zoster was less certain.

- However, the US data should be interpreted with care. Varicella was removed from the national disease list in 1991 and was designated notifiable again in 2002. In the period from early 1990s to early 2000s, only 3 areas in 3 states (out of the total 50 states) were included in the active surveillance project. The data from CDC is on a voluntary basis from passive reports.

- US post-licensure epidemiology studies showed that there was an association between increase in varicella vaccine coverage and decrease in VZV disease burden but a causal relationship could not be established from these cross-sectional studies.

5.2.2 Japanese Experience

Information about varicella in Japan was obtained from the Ministry of Health, Labour, and Welfare (MHLW) Department (http://www.mhlw.go.jp/english/index.html) and the Infectious Disease Surveillance Center, National Institute of Infectious Diseases of Japan (IDSC, NIID) (http://www.nih.go.jp/niid/index-e.html).

Background

Varicella vaccine was licensed in Japan in September 1986 to both healthy and high risk group children. It was introduced as voluntary vaccination for children ≥ 1 year of age since 1987.(164) A total of 2,710,000 doses were distributed between 1994 and 2002. As VZV is heat labile, the current Biken varicella vaccines used in Japan contains high dose (20,000-30,000 pfu/ dose) of vaccine virus.(123) Varicella is not a notifiable disease in Japan.(165) It is reported as a sentinel reporting disease to the national Infectious Disease Surveillance Center.(166)

Epidemiology and Vaccine Coverage

There were 160,000- 260,000 new cases of varicella in Japan in recent 10 years. Infants and children <10 years accounted for 10% and 95% of all cases of varicella in Japan in the past 20 years respectively. Proportion of 1-4 years is increasing while that of 5-9 years is decreasing. Since 1995, children ≤ 5 years accounted for 90% of all cases (**Figure 25**).

Data on population of Japan was obtained from MHLW. Data on number of varicella cases was searched from IASR (Infectious Agents Surveillance Report), IDSC. Information on years 1982-2005 was obtained.(167) Estimated incidence rate (all ages) was displayed in

Table 39.There was a gradual decrease in overall incidence rate (all ages) parallel with decline in paediatric population from 180-220 per 100,000 population in 1980s to 130-150 per 100,000 population in late 1990s in Japan until 1999, when incidence started to rise (**Figure 26**). However, according to the IDSC, this apparent rise was due a shift of change of reporting centres in the same year. The current problem of varicella vaccination in Japan is low vaccine coverage rate. The overall vaccine coverage rate was only 25-30%. Some regions even had even lower coverage rate, around 8-13% in nursery school children.(164)

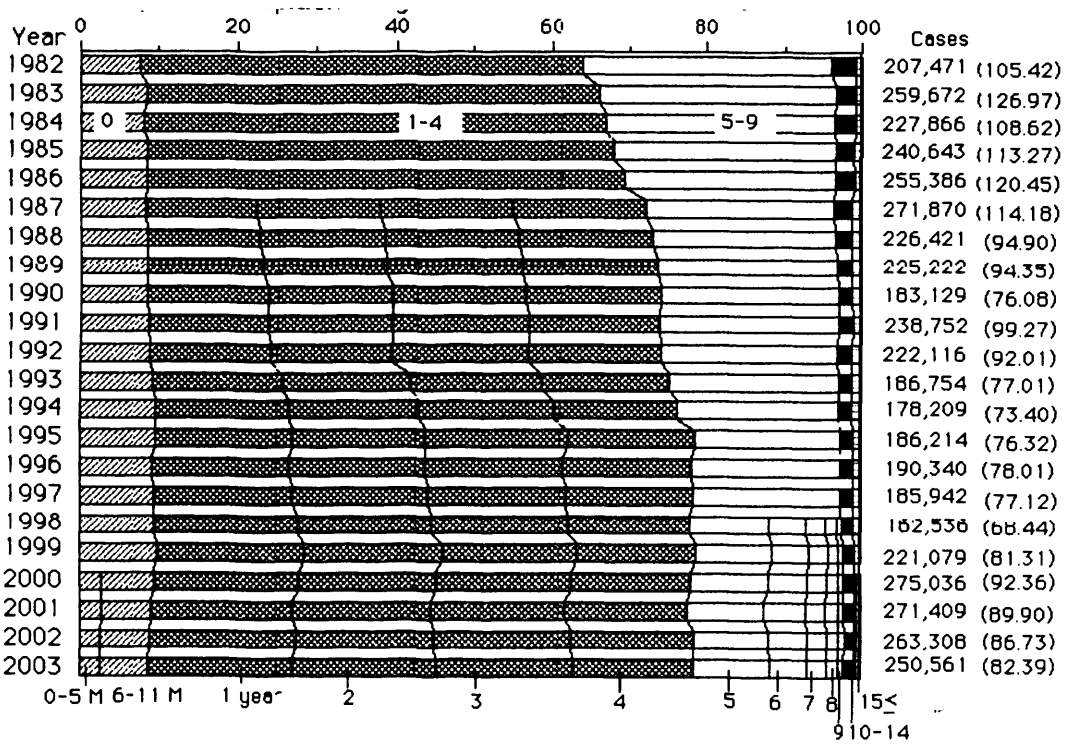


Figure 25: Distribution of varicella in children < 9 years, Japan, 1982-2003.

Source: NIID(166), Japan.

Year	Cases	Population	Rate*
1982	207,471	118,008,000	176
1983	259,672	118,786,000	219
1984	227,866	119,523,000	191
1985	240,643	120,265,700	200
1986	255,386	120,946,000	211
1987	271,870	121,535,000	224
1988	226,421	122,026,000	186
1989	225,222	122,460,000	184
1990	183,129	122,721,397	149
1991	238,752	123,102,000	194
1992	222,116	123,476,000	180
1993	186,754	123,788,000	151
1994	178,209	124,069,000	144
1995	186,214	124,298,947	150
1996	190,340	124,709,000	153
1997	185,942	124,963,000	149
1998	162,536	125,252,000	130
1999	221,079	125,432,000	176
2000	275,036	125,612,633	219
2001	271,409	125,908,000	216
2002	263,308	126,008,000	209
2003	250,561	126,139,000	199
2004	245,941	126,176,000	195
2005	242,217	126,210,000	192

Table 39: Reported cases and estimated crude incidence rate of varicella in Japan, 1982-2005.

* Per 100,000 population.

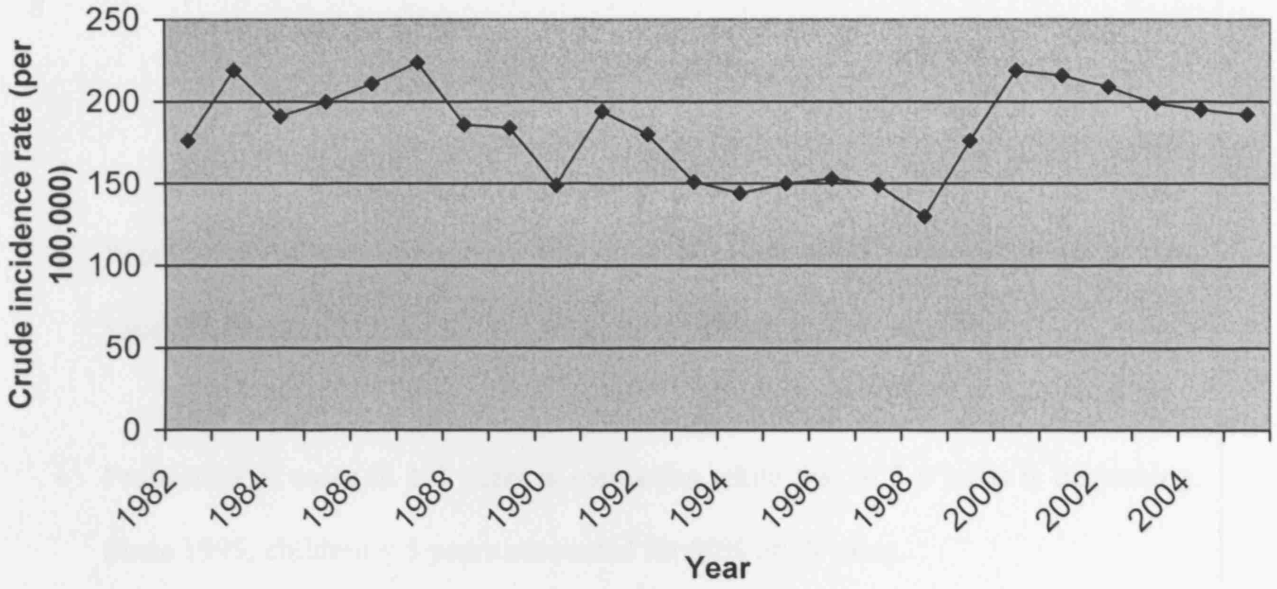


Figure 26: Crude incidence rate (per 100,000 population) of varicella reported in Japan, 1982-2005.(166)

* Incidence rate per 100,000 population.

** Incidence rate per sentinel clinics.

Source: NIID, MHLW(166)

Key Messages

- Potency of varicella vaccine used in Japan is higher (20,000-30,000 pfu/dose) than vaccines licensed in UK (1,300-1,995 pfu/ dose).

- Proportion of cases in 1-4 years is increasing while that of 5-9 years is decreasing. Since 1995, children $\leq$ 5 years accounted for 90% of all cases.

- There was decrease in average incidence rate from 180-220 per 100,000 population in 1980s to 130-150 per 100,000 population in late 1990s with a parallel decline in paediatric population in Japan until 1999.

- An apparent rise in incidence was observed since 1999 but whether this was a true rise was not sure because of a change of reporting system in the same year.

- Varicella vaccine coverage was only 25-30% in Japan, with a possibility that some vaccinees were protected from breakthrough diseases because of booster by subclinical infections with wild-type VZV.

6 Parental Acceptability

Mathematical model demonstrated that vaccine coverage of at least 70% was required to have long term benefit of decrease disease burden.(147) From the experience in US, varicella declined in areas with at least moderate coverage (70%).(168) WHO emphasised that it was important to ensure high vaccination coverage rate to prevent changes in the epidemiology.(9) Therefore, when considering a national vaccination programme it is important to consider whether parents are likely to accept the new vaccines. The decision to immunisation is a very complex and dynamic process. Many factors affect whether a parent will immunise their children. Among these are the perceived severity of the disease and the safety and efficacy of the vaccine.(169)

Investigations of parental attitudes to varicella vaccine will help to predict the acceptability of this vaccine. Studies in US, Canada, and Australia where varicella vaccine was recommended for children as routine immunisation (either as public or self funding programmes) indicated that a lack of knowledge about varicella and varicella vaccine was an important factor of low vaccine coverage. Parents were not very concerned about lost time at work. Perceived severity of varicella, safety, efficacy and duration of protection provided by varicella vaccine, and the number of injections children received were key factors. Lay media and health care providers were the main sources of information for parents.(170-174)

Vaccine coverage rates in US and Japan, the two countries having the longest history of recommended varicella vaccination, are discussed in this section.

Experience from US: vaccine coverage under public funding

Report of varicella coverage rate was available from US CDC. It was first measured in 1996. Annual varicella coverage rate in children 19-35 months, the main target group of the US immunisation programme, increased from 16% in 1996 to 88% in 2004 (**Figure 27**).(44)

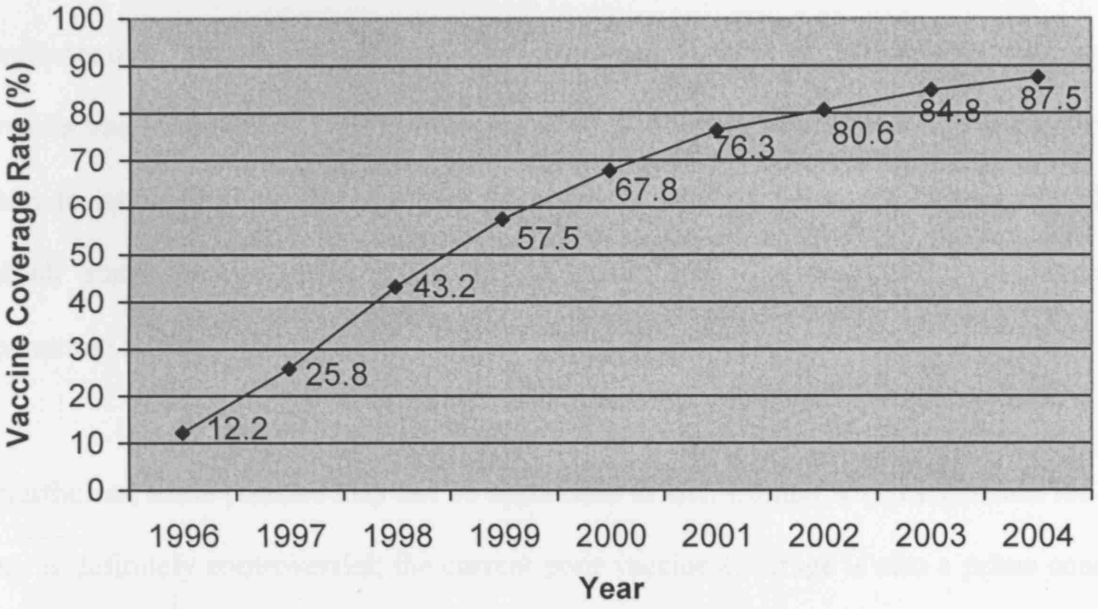


Figure 27: Estimated national varicella vaccine coverage rates in 19-35 months old children in US, 1996-2004. Source: The Pink Book (Appendix G), CDC.(44)

Experience from Japan: vaccine coverage without public funding

Very limited information was found. Varicella vaccine was introduced in 1987 as voluntary immunisation for children ≥ 12 months in Japan. The average varicella vaccine coverage was only 25-30% 20 years after it was licensed in Japan.(164) Some areas even had coverage rate as low as 8-13%. There was worry that the current coverage rate was insufficient to prevent epidemics.

US carried out several methods to ensure high varicella vaccine coverage. An increasing rate was seen since the implementation of compulsory requirement for day care and school entry for 33 states and the District of Columbia implemented from 1997 to 2002. Study found that this mandate increased vaccine uptake by 8%.(175) Another policy was the simultaneous administration with other vaccines. Among US children who received varicella vaccine, 86% received another vaccine simultaneously. Most commonly, children received varicella vaccine simultaneously with MMR vaccine. This was seen in 70% of all children who received varicella vaccine in 2004.(176) In 2005, the US ACIP recommended school entry requirement policy to included kindergarten to college students. By July 2006, the District of Columbia and all states except Idaho, Montana, Vermont, and Wyoming had implemented this programme.(125)

Nevertheless, these policies may not be applicable to UK. Compulsory vaccination for school entry is definitely controversial; the current poor vaccine coverage is also a prime concern in UK. In the annual COVER report 2004/05 which summarised vaccine coverage rates in 1995-2005, UK was found failing to reach WHO target vaccine coverage level of 95% for any antigen.(177) The problem is especially serious in the case of MMR vaccine. Among all vaccines included in the current childhood immunisation programme in UK (**Appendix G**), MMR has the lowest coverage rate (**Figure 28**).(178) This phenomenon was seen since the publication of a study reported association between onset of developmental regression and MMR vaccination in 1998.(179) Despite the fact that the study itself did not confirm a causal relationship nor did subsequent thorough researches carried out in different countries, public confidence has not yet been regained.(169) In 2004/05 the coverage rate for MMR in UK was only 82%.

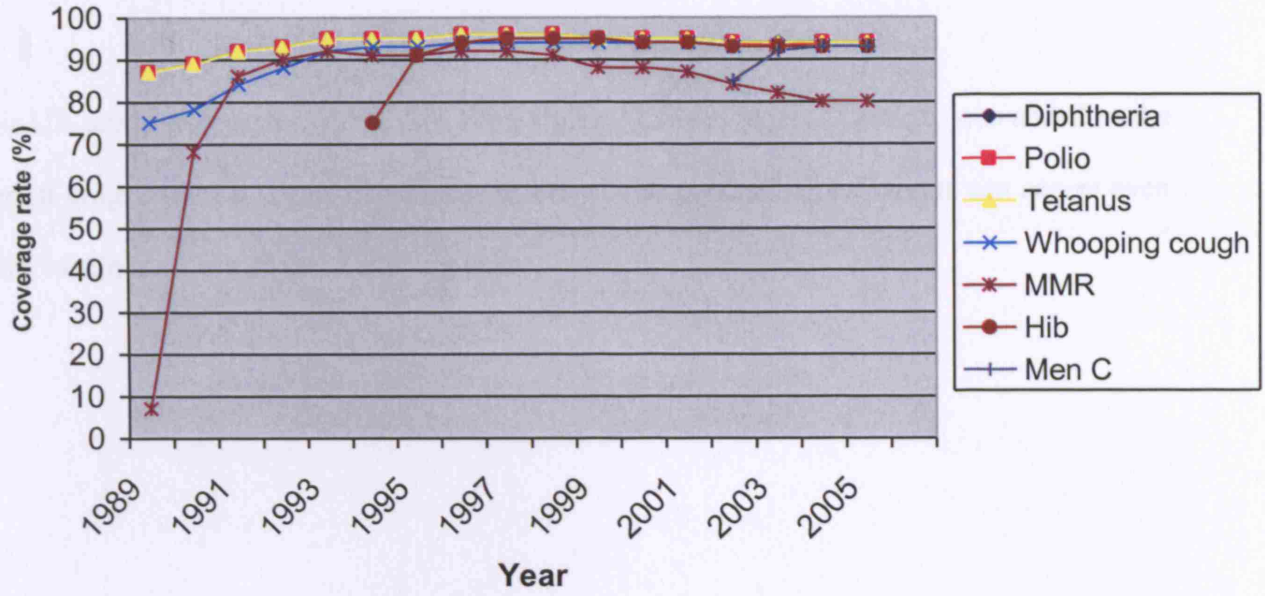


Figure 28: Estimated vaccine average rate in children at 2 years of age in England and Wales, 1989-2005.(178) Source: HPA.

In a recent survey in 2004 to investigate parental attitudes to existing and new vaccines in UK, varicella was perceived as the least serious disease among the six vaccine preventable diseases investigated (the other five were meningitis, measles, diphtheria, whooping cough, and influenza).(180) Even if varicella vaccine was provided routinely, only about 40% parents would accept it. Majority of parents who would accept varicella vaccines rated varicella as very serious or serious disease. 53% parents preferred new vaccines to be given separately rather than as combination vaccines with existing vaccines because of worry of vaccine overload. They believed that combination vaccines were less safe. About 60% parents accepted no more than two injections on any one occasion. Nearly 80% parents thought that

the current childhood immunisation programme included the right number of vaccines for their children.

This UK study was performed before extra vaccine, pneumococcal vaccine, was added to the current programme. It seems that a large effort will be needed before parents can accept even more vaccines on top of these existing ones.

Key Messages

- UK is failing to reach WHO target level of 95% vaccine coverage for any single antigen.

- From experience in other countries, perceived severity of varicella, safety, efficacy and duration of protection provided by varicella vaccine are key factors affecting varicella vaccine coverage.

- Varicella is perceived as a mild disease by parents in general in UK.

- Majority of British parents thought that the current childhood immunisation programme included the right number of vaccines for their children.

- Even if vaccine is to be provided free, only 40% British parents would accept varicella vaccine.

- Given the current context in UK, it is unlikely that parents are going to accept varicella vaccine at the moment.

7 International and National Positions on Varicella Vaccine

WHO

The only WHO position paper on varicella vaccine was published in1998.(9) It was suggested that routine childhood immunisation against varicella might be considered in countries where VZV infection was a relatively important public health and socio-economic problem, where the vaccine is affordable, and where high (85%-90%) and sustained vaccine coverage could be achieved. It was also recommended that routine immunisation in children must emphasise high vaccine coverage to avoid shifting the disease to older age groups.

UK

Varicella vaccines were recommended for health care workers and healthy susceptible contacts of immunocompromised individuals only.(43) The programme for health care worker was recommended in 2003 by the Joint Committee on Vaccination and Immunisation (JCVI) for seronegative individuals who had direct patient contact with patients to receive 2 doses of varicella vaccines 4-8 weeks apart.(100) At present there is no plan to give varicella vaccine to all children routinely. The rationales are;(43)

- Potential increase in age of those acquiring infection.
- Potential increase in number of cases of shingles.

The potential use of varicella vaccine in UK is regularly reviewed by the Joint Committee on Vaccination and Immunisation (JCVI). The latest meeting that mentioned varicella vaccine was held on 22/6/06. The committee discussed modelling studies on the vaccine and found that the studies suggested increase incidence of varicella in adults over time if infant immunisation programme was to be offered. Findings implied benefits natural infection resulted in herd immunity. Vaccination in older adults resulted in decrease in incidence of zoster.(181) The committee decided to wait for more evidence before any further recommendation could be made.

8 Further Discussion

Many new vaccines are available now and even more are on the waiting list to add to the market. The decision to which new vaccine should be added to the national immunisation programme depends on both policy concerns and programmatic issues.

Varicella vaccination is unlikely to be a priority in developing world. However, its potential use in developed countries is becoming a debating topic. In Europe, the European Sero-Epidemiology Network (ESEN) was established in 1996 to coordinate surveillance of vaccine preventable diseases.(182) The European Sero-Epidemiology Network 2 (ESEN 2) was formed later on the basis of ESEN. VZV infection was identified as one of the eight target diseases. The other seven diseases are measles, mumps, rubella, pertusis, diphtheria, hepatitis A, and hepatitis B. Currently there were 22 European countries (including UK, Italy, Spain, Greece, Belgium, Czech Republic, Finland, Germany, Netherlands, Sweden, Republic of Slovenia, Romania, Ireland, Israel, and Bulgaria) and Australia involved in the network.(183)

When compared with other developed countries like US, Canada, Australia, and Germany, UK seems rather hesitant in including varicella vaccine in the routine childhood immunisation programme. Nevertheless, this is supported by the following concerns.

First of all, the impact on the long term epidemiology of VZV infection, both varicella and zoster, is still unknown. In UK, overall disease burden of varicella is now shifted to preschool children 1-4 years. This group has the lowest complication and case fatality rate. There is a

risk that mass immunisation may shift the burden to older groups if vaccine efficacy wanes with time, resulting in higher morbidity and mortality. This is especially worrisome in view of the ageing British population as a result of decrease in both birth rate and mortality rate. According to WHO, the very old (≥ 80 years) are the fastest growing population in developed countries.(184) Upward shift of VZV infection will result in even more disease burden. There is also a theoretical risk of increase in zoster if exogenous exposure to VZV infection is reduced. Despite post-licensing surveillance in US reporting no increase in zoster in adolescents and adults after 10 years, it is too early to predict the impact on zoster. The exact latency period of VZV infection is not clear. Study reported that the average time to develop reactivation is 2-6 months after onset of immunosuppression,(185) such as in elderly or those on immunosuppressant. Other study suggested an average of 5-40 years.(186) Thus it may take decades to see any change in epidemiology of zoster.

Secondly, there are concerns about varicella vaccines. It seems that varicella vaccine is effective at modifying the disease severity but not potent enough to prevent infection. Outbreaks occurred from time to time in day care centres and schools in US. In June 2006, the US Advisory Committee on Immunisation Practices (ACIP) just announced a change in the recommendation from one- dose to two- dose regimen for children < 13 years. A booster dose was offered to children 4-6 years, i.e. first dose at 12-15 months and a second dose at 4-6 years of age.(187;188) Canada tried another strategy to reduce waning of vaccine efficacy. Ontario changed the routine schedule from 12 months to 15 months in 2005 following recommendations from NACI.(189) However, whether vaccination of children at an older age can prevent outbreaks is still unknown.

9 Conclusion

Varicella zoster virus infection is an important public health problem in UK. It is associated with significant disease morbidity and mortality. Economic lost due to this infection is not negligible. Mass immunisation of young children will be the best strategy to eliminate this disease. However, given the current evidences with theoretical risk of epidemiological shift of disease burden to older age groups who have higher complication and mortality rates, the possibility of increase in incidence of zoster which is the main disease burden of VZV infection, the uncertain duration of vaccine protection, and the low expected parental acceptability, it is not justified to include varicella vaccine in the routine childhood immunisation programme in UK at the moment.

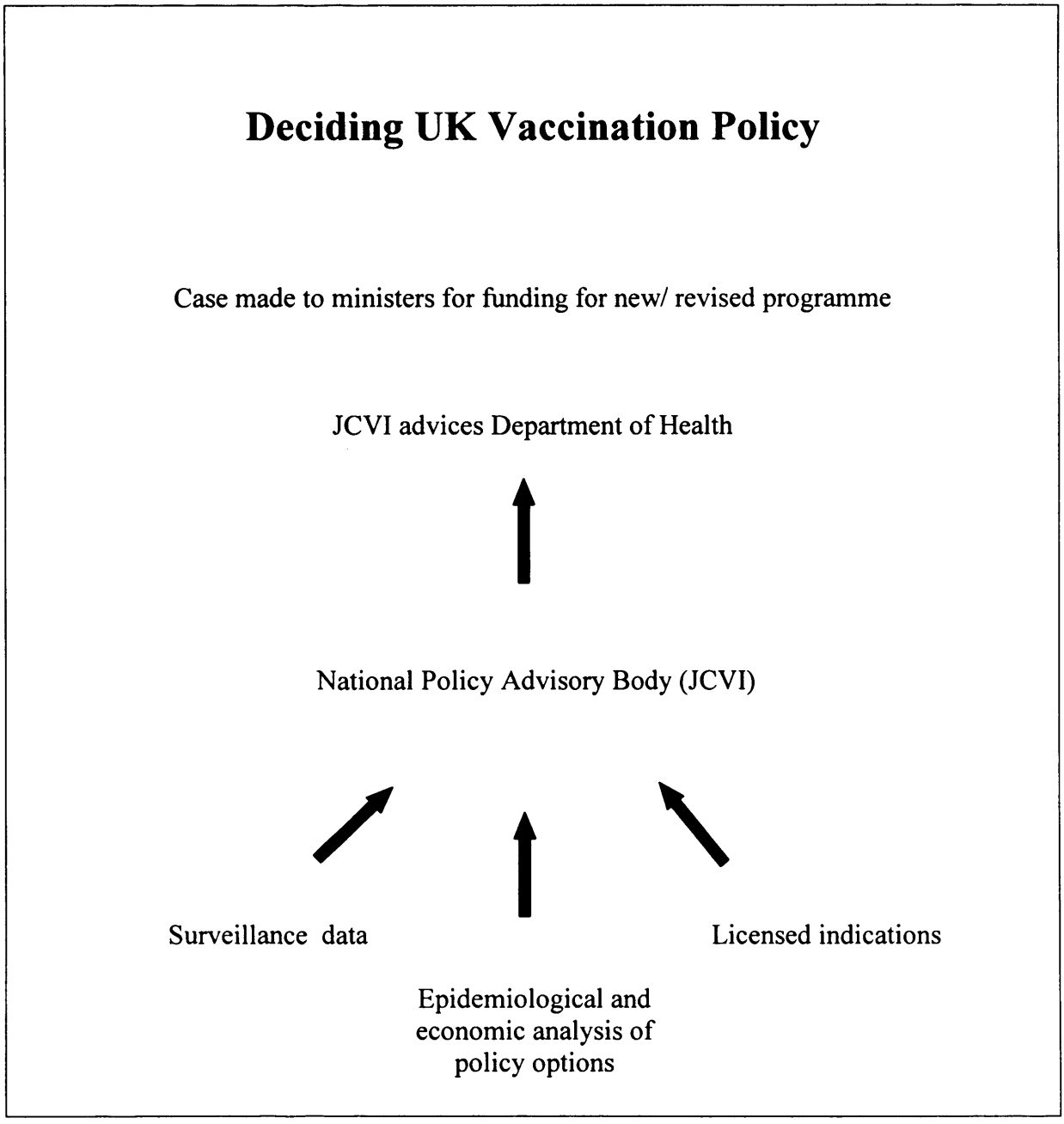
10 Limitations

Though every effort has tried to gather information for this thesis, there are several limitations because of limited time and unfamiliarity with the British system. Epidemiological data came mainly from England and Wales, limited information about statistics in Scotland and Northern Ireland was included. Other resources might be available. However, in view that the population of England and Wales contributes to nearly 90% of total UK population, data on England and Wales should be representative of the whole country (see **Appendix H** for distribution of UK population in 2004).(190)

Searching was performed on PubMed but not on EMBASE because of unfamiliarity with the latter database. It would be better to include both sources if time was allowed. This is because EMBASE has a more European focus while PubMed is more American with about 40% overlap.(191) However, the epidemiology part of this thesis included also data from official British websites such as HPA, RCGP, SCIEH, and CDSC (NI). The effect of not including searching from EMBASE in this part is minimised. In the second part, studies about varicella vaccines came essentially from US. In addition, evidences were supplemented by international reviews and thus bias is hopefully reduced. Moreover, large- scale studies are expected to appear in both databases. Japan has the longest history of using varicella vaccine. It is ideally better to include as much Japanese studies as possible, especially the long term ones. Large and important studies are expected to be translated to English. Disappointingly, only very few publications were identified. It is not sure if more studies can be found using EMBASE. Nevertheless, researches reported that VZV strains circulating in UK are different from those in Japan. Though there is only one serotype of VZV worldwide, geographical

variations exist among wild-type viruses in different countries. VZV can be divided into two clades, the European/ American strain and the Asian strain. At least 3 genotypes, strain A, B, and C, have been identified so far. Type C is the common type circulating in UK, with smaller proportion of type A and B. The major genotype in Japan is type B.(192-194) It is therefore not clear if results of studies on Asian populations can be generalised to European populations.

Appendix A: How is UK Immunisation Policy Decided?



Source: NHS.(6)

Appendix B: Method

Disease Epidemiology

Epidemiological data on VZV infection in UK were available through 2 sources according to HPA(43): cases reported to the Royal College of General Practitioners by sentinel GP practices in England and Wales (http://www.rcgp.org.uk/bru/index.asp) and in Scotland through statutory notifications (http://www.show.scot.nhs.uk/scieh/). Information about Northern Ireland was obtained from the Communicable Disease Surveillance Centre of Northern Ireland (http://www.cdscni.org.uk/default.asp).

More epidemiological studies were identified through **PubMed** using the words "**Varicella** OR **Chickenpox**", "**Epidemiology** OR **Incidence** OR **Prevalence**", "**United Kingdom** Or **England** Or **Wales** or **Scotland** Or **Northern Ireland**" ". Studies were limited to "**Humans**" and "**English**". This resulted in 96 papers. Similar research strategies were used for zoster using the word "**Zoster**" which resulted in 69 papers. For the epidemiological data to be representative, only articles with data at a population level (UK as a whole, or any of the 4 UK countries) were included in this thesis. Searching started in January 2006 and completed in March 2006.

Economical Considerations

As the structure of health care systems and the costs of health care can be very different from country to country, economical evaluation of VZV infection included only UK studies. **PubMed** was searched using the words "**Varicella** OR **Zoster**" and "**Cost**" and "**United Kingdom**" with limitations to "**Humans**" and "**English**". No other limitation was applied. This resulted in 18 papers. All papers mentioned about overall financial burden of VZV infections in UK were included. Papers concerned only specific part of health costs, such as estimation on drug therapy, were excluded. Finally 4 articles were included.

Alternative Strategies

UK national guidelines on treatment of VZV related diseases were searched using the words "**Varicella**" or "**Chickenpox**" from the National Health Service (**NHS**) Guidelines Finder Specialist Library (http://www.library.nhs.uk/guidelinesfinder), Department of Health (http://www.dh.gov.uk/Home/fs/en), and Health Protection Agency (**HPA**) (http://www.hpa.org.uk). Review articles were searched from **Cochrane Library** database and **BMJ Clinical Evidence**.

Varicella Vaccines

Reviews

These were searched from the **Cochrane Library**, **BMJ Clinical Evidence**, and reviews of international expert groups.

1) Cochrane Library (http://www.nelh.nhs.uk/cochrane.asp)

Searching was done using the words "**Varicella**" or "**Chickenpox**". No limitation was added. This resulted in two papers. One if them was a review on antiviral drug, acyclovir.(86) The other was a proposed protocol on varicella vaccine.(195) The protocol was proposed in 1999 but had not yet finished.

2) BMJ Clinical Evidence (http://www.clinicalevidence.com/ceweb/conditions/index.jsp)

Review about varicella vaccine was found under the topic "**Chickenpox**" which was under the section "**Infectious diseases**". One review on healthy children by Swinger was available.(196)

3) International Expert Reviews

Searching was performed from the websites of WHO (http://www.who.int/en), US CDC (http://www.cdc.gov), PHAC (http://www.phac-spc.gc.ca) and CTFPHC (http://www.ctfphc.org).

Clinical studies and Meta-analysis

Further studies were searched from **PubMed** used the words "**Varicella Vaccine**". Studies were limited to "**Humans**", "**English**", and "**All Child, 0-18 years**". Studies types were limited to "**Clinical Trials**", **Meta-analysis**", **Randomised Controlled Trials**". No further limitation was added on searching strategy. Searching was completed in June 06. 76 articles were identified. Only studies included healthy children were selected, this resulted in 42 papers. All those with abstracts were reviewed. Exclusion criteria: studies included only adolescents and adults (1 paper), studies on combination vaccines (8 papers), sample size <500 (16 papers). Due to limitation of time, articles without full papers were also excluded

(13 papers). This resulted in 4 papers. Information on 3 articles without full papers was obtained from BMJ Clinical Evidence. Thus finally 7 papers were available. The paper by Lau et al was a study comparing the vaccines by Oka/ Merck (Varivax) and Oka/ RIT (Varilrix) and would be mentioned in the section "Varilrix".

Oka/RIT (Varilrix)

Searching using the words "Varicella Vaccine" resulted in studies mainly concerned about Oka/Merck. As Oka/RIT is also licensed in UK, efficacy and safety of this vaccine was as important as Oka/Merck. Thus additional searching was performed for this vaccine separately. Studies were searched from **PubMed** using the words "**Varilrix**" or "**Oka/RIT**" with limitations to "**Humans**", "**English**" and "**All Child: 0-18 years**". Searching was finished in June 06. Only 25 papers were available. As the number of articles available was very limited, sample size required in these studies was reduced to $\geq$ 100 (2 papers excluded). Only studies included healthy individuals were included (8 papers excluded). This resulted in 15 papers. Exclusion criteria: no full papers were available (8 papers), studies included only adolescents and adults only (1 paper), studies on combination vaccines (1 paper), vaccines as post-exposure prophylaxis (2 papers). Finally only 3 articles left (Sheffer et al, 2005, Passwell et al, 2004, and Lau et al, 2002).(90;136;137)

Combination Vaccines

Searching was performed from **PubMed** using the words "**Measles, Mumps, Rubella, and Varicella Vaccine**" with limitations to "**Humans**", "**English**" and "**All Child 0-18 years**" in June, 06. Study types were limited to "**Clinical Trials, Meta-analysis, and Randomised Controlled Trials**". This resulted in 24 papers. As no combination vaccine is licensed in UK currently, this is not the focus of this thesis. Only large scale studies with sample size $\geq$ 1000

were included (10 papers excluded). This was because combination varicella vaccines were not the focus of this thesis as none of these vaccine was licensed in UK.(43) Only studies involved healthy children were included (1 paper excluded). This resulted in 13 potential articles. Articles were further excluded if: concomitant administration of vaccines other MMR (4 papers), full papers not available (7 papers). Finally only 2 papers were included (Lieberman et al 2006 and Shinefield et al 2005).(142;143)

Japanese Studies

PubMed was searched used the terms "**Varicella Vaccine**" and "**Japan**" with limitations to "**Humans**", "**English**" and "**All Child: 0-18 years**". No other limitation was added. This resulted in 37 papers. 36 papers were excluded: not Japanese studies or not varicella vaccine (for example reviews by Japanese authors or other vaccines available in Japan) (19 papers), no full paper available (10 papers), studies not on healthy children (3 papers), and vaccine as post-exposure prophylaxis (1 paper). Only studies with long term outcomes were included as short term effects such as anaphylaxis/ allergy were sufficient from US studies (3 papers excluded). Only 1 paper was included finally.(124) 2 extra papers were provided by Dr Helen Bedford.(118;123)

Outbreak Studies

These were obtained from US CDC using the words "**Varicella outbreaks**".

Appendix C: Calculation of Consultation Rate

$$\text{Consultation rate (per case)} = \frac{\text{Number of consultations}}{\text{Number of cases}}$$

England and Wales

1) From RCGP annual report 2004.(21)

Age (years)	Number of cases	Number of consultations	Estimated consultation rate (per case)
<1	211	291	1.4
1-4	1134	1625	1.4
5-14	460	715	1.6
15-24	67	105	1.6
25-44	168	294	1.7
45-64	22	39	1.8
65-74	4	7	1.8
≥ 75	4	7	1.8
All ages	**2070**	**3083**	**1.5**
M	1025	1555	1.5
F	1045	1528	1.5

Number of varicella cases, consultations, and consultation rate (per case) in England and Wales, 2004.

2) From Brisson et al.(20)

Age (years)	Number of cases	Number of consultations	Estimated consultation rate (per case)
0-4	344,662	148,754	0.4
5-14	224,242	73,482	0.3
15-44	95,730	49,306	0.5
45-64	4,945	2,642	0.5
≥ 65	1,289	1,103	0.9
Overall	**670,868**	**275,286**	**0.4**

Number of varicella cases, consultations, and consultation rate (per case) in England and Wales, 1991-2000.

Scotland

From Bramley et al.(28)

Age (years)	1996			1997			1998		
	Incidence rate	Consultation rate	Consultation Rate (per case)	Incidence rate	Consultation rate	Consultation Rate (per case)	Incidence rate	Consultation rate	Consultation Rate (per case)
< 1	2692	2060	0.8	3503	2646	0.8	3217	2133	0.7
1-4	5141	4241	0.8	6344	4261	0.7	6031	4227	0.7
5-14	1381	953	0.7	1589	987	0.6	1407	911	0.6
15-24	240	319	1.3	234	256	1.1	197	211	1.1
45-64	18	44	2.4	20	24	1.2	20	36	1.8
≥ 65	15	23	1.5	11	13	1.2	8	12	1.5
All ages	**556**	**457**	**0.8**	**652**	**464**	**0.7**	**590**	**435**	**0.7**

Incidence rate (per 100,000 population), consultations rate (per 100,000 population), and consultation rate (per case) of varicella, 1996-1998.

*Incidence rate for the age 25-44 years could not be calculated as individuals were regarded as2 groups when mentioning about incidence rate but grouped as one group when mentioning about consultation rate.

Appendix D: Studies on Varicella Vaccines

A) International expert reviews

WHO

1) **WHO position paper** (9)

In this position paper in 1998, there was a brief review of varicella vaccines based on both US and Japanese studies.

2) **Vaccine safety review** (Supplementary information on vaccine safety, part 2: background rates of adverse events following immunization) (106)

This WHO document reported adverse events following immunisation of the most commonly use vaccines. Varicella vaccine was one of the 20 vaccines being reviewed.

3) **GACVS report** (Global Advisory Committee on Vaccine Safety report) (133)

GACVS was an expert advisory body established by WHO to deal with safety of new or developing vaccines of global importance. Varicella vaccine was reviewed in June 2006. About 50 million doses of varicella vaccines were administered in US in the 11-year (1995-2006) reviewed period.

US CDC

1) **The pink book** (Epidemiology and prevention of vaccine preventable disease) (44)

A handbook published by CDC with general information on immunisation and vaccine preventable diseases.

2) **MMWR summary** (Morbidity and Mortality Weekly Report summary: surveillance for safety after immunization: VAERS-US, 1991-2001) (107)

This report summarised the adverse events reported to the US post-licensing surveillance system, the Vaccine Adverse Events Reporting System (VAERS), in the first 6 years following introduction of routine varicella immunisation (1995-2001). See **Appendix D** for brief introduction of VAERS.

Canadian reviews

1) **CTFPHC review** (Use of varicella vaccine in healthy populations, systematic review and recommendations by the Canadian Task Force on Preventive Health Care)(110)

This was a systematic review to evaluate effectiveness and side effects of varicella vaccine in healthy individuals.

2) **NACI review** (National Advisory Committee on Immunization update on varicella) (75)

This was a review by the Canadian NACI in 2004 with update on VZV infection and varicella vaccines.

B) Key papers

1) Wise et al, 2000 (108)

This was a review on reported adverse cases from the US VAERS in the first 3 years (1995-1998) after licensure. Different from the MMWR summary above, this study included data from previous published studies, manufacturer's post-marketing studies, and the US pregnancy registry for Varivax (a collaboration by CDC and vaccine manufacturer to follow

the outcomes of pregnancy when women are vaccinated within 3 months before pregnancy or at any time during pregnancy).(197) About 9.7 million doses of Varivax had been sold and 6,574 adverse reports received in the study period. 82% received Varivax alone, 12% were given with MMR, and the remaining given with other vaccine combinations.

2) Sharrar et al, 2000 (109)

This study used data from the vaccine manufacturer (Merck)'s post-marketing surveillance system, the Worldwide Adverse Experience System (WAES), to summarise adverse events in the first 4 years (1995- 1999) following licensure. 16 million doses of varicella vaccines were distributed and 7,963 cases reported to the system in the study period. Additional reports were obtained from published literatures. See **Appendix E** for brief introduction of WAES.

3) Weibel et al, 1984 (116)

Full paper was not available from PubMed. However, information was supplemented by BMJ Clinical Evidence.(198) The study was a double blind, placebo controlled trial with 956 healthy children aged between 1-14 years in Pennsylvania, US. Finally 914 children (96%) confirmed seronegative and were included. 468 children (51%) received the Oka/ Merck vaccines and the other 446 (49%) received placebos.

C) Other Clinical Trails and Meta-analysis

1) Kuter et al, 1991 (122)

This was a follow-up study of Weibel et al's cohort in US. Follow-up period was 7 years. The main aim of the study was estimation of vaccine efficacy and risk of breakthrough diseases.

2) Ngai et al, 1996 (111)

This was a large scale multi-centre randomised clinical trial carried out in Philadelphia to study the safety and immunogenicity of one versus two doses of varicella vaccines in healthy children. 2,196 children aged 12 months and 12 years (median age 43 months and 47 months for one- and two- dose regimen respectively) participated in the trial. The study started in 1991. Follow-up period was 9 months. Vaccines used were Oka/ Merck, 2,900-9,000 pfu. 1,103 and 1,093 children were randomised to receive one and two injections of varicella vaccine given 3 months apart respectively.

3) Varis et al, 1996 (119)

Full paper was not available. Limited information was obtained from abstract and BMJ Clinical Evidence.(198) This was a randomised controlled study in 513 healthy children aged 10-30 months in Finland. Children were randomly allocated into 5 groups to receive four different lots of vaccines (high titre and low titre) and placebo (exact potency of vaccines not clear).

4) Brisson et al, 2000 (121)

This was a meta-analysis using mathematical model based on published studies and unpublished data from Merck Research Laboratories to study breakthrough rate. Vaccines used were Oka/ Merck, 1000-1625, 2900-9000, and 17,430 pfu/ dose.

5) Kuter et al, 2004 (117)

This was a follow up study of Ngai et al.(111) Enrolment continued after the initial 9-month study in 1991. Finally 2,216 children aged 12 months to 12 years were enrolled. Study period was 10 years. Other details same as mentioned above.

D) Japanese Studies

1) Asano et al, 1994 (118)

This was a study in early 1990s. It was a follow-up 20 years after 244 healthy and sick individuals received experimental varicella vaccines of Oka strain in 1974-1976. The vaccinees aged 10 months to 13 years at the time of vaccination. They were already adolescents and adults by the time the study was performed. Questionnaires were sent to parents or guardians of the 244 vaccinees to ask about history of exposure to natural varicella, breakthrough diseases and zoster since vaccination. Response rate was 39% (96/244). Of these 96 participants, immunologic tests for humeral (VZV antibody level) and cellular immunity (skin test) were conducted in 26% (26/96) individuals. The potency of vaccine used was not mentioned in this study but published elsewhere. However, full papers of those studies were not available.

2) Ozaki et al, 2000 (124)

This was a follow-up study of 973 healthy individuals aged 1-32 years (mean age 3 years) by questionnaires 10 years after received vaccination between 1987 and 1997 at a paediatric clinic. The vaccine used contained a minimum of 1,000 pfu/dose (but maximum potency not mentioned). Questionnaires were sent to parents of 860 initially seronegative individuals in 1998.

3) Takahashi et al, 2001 (123)

This was a review of Japanese studies in 2001 by Dr Takahashi 25 years after his development of Oka vaccine.

Appendix E: US Post-licensing Vaccine Surveillance System

There are two main post-licensing surveillance systems for safety of varicella vaccine in US. One, the Vaccine Event Reporting System (VAERS), is a nationwide vaccine safety surveillance system jointly operated by the FDA and CDC.(199) It receives reports from the vaccine manufacturer, health care professionals, and patients. The other, the Merck's Worldwide Adverse Experience System (WAES), is a database containing voluntary reports of adverse responses from health professionals and consumers to the drug company. All reports finally will be submitted to the US VAERS. Both systems are passive surveillance systems relying on voluntary reports. It is estimated that WAES contributes 75% of all reported cases in VAERS.(109) Reported rates are not suggested to be interpreted as incidence rates in view of the possibility of under or over reporting in these passive surveillance systems.(108)

Appendix F: Definition of Adverse Events

VAERS and WAES: Events reported to the VAERS are according to the US National Childhood Vaccine Injury Act of 1986. It requests health care workers to report any event listed by the vaccine manufacturer as a contraindication to subsequent doses of the vaccine and any event listed in the Reportable Events Table that occurs within the specified time period after vaccination. In the case of varicella vaccine, this means events and interval as described in manufacturer's package insert as contraindications to additional doses of vaccine.(200) Both VAERS and WAES system define severity of adverse events according to definition set by US CDC. Serious events as those involving deaths, life threatening illness, hospitalisation or prolongation of hospitalisation, and permanent disability.(44) Mild events can be: fever, mild rash, and local reaction such as soreness and swelling. Moderate events include: febrile convulsion. Severe events include: pneumonia, encephalopathy, and thrombocytopenia.(113)

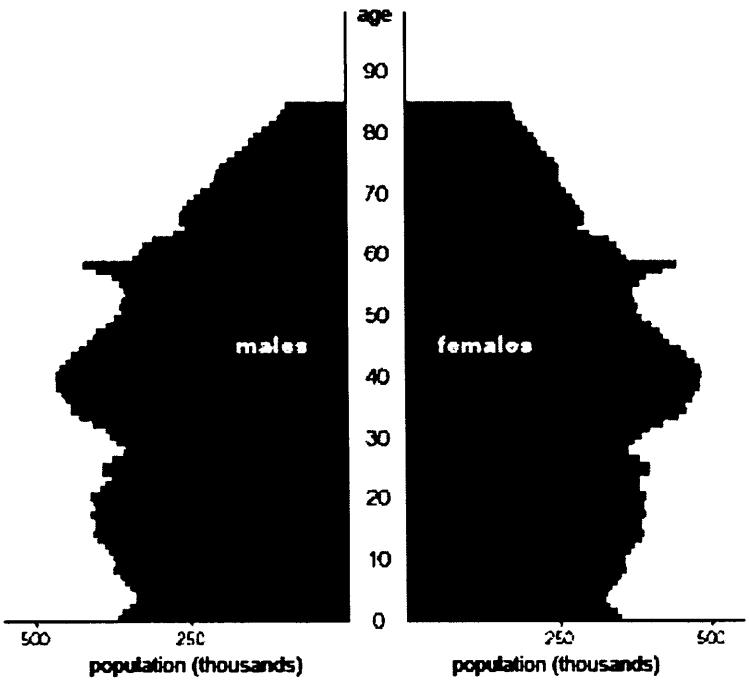
WHO defines serious reaction is one that results in death or hospitalization. Mild reaction is one that is not serious.(201) Mild events include local reactions (for example pain, swelling, and redness), fever, rash, and systemic symptoms (such as irritability, malaise, "off-colour", and loss of appetite). Serious reactions include anaphylaxis, neurological (such as seizure, encephalopathy), thrombocytopenia, persistent inconsolable screaming (> 3 hours).(112)

Appendix G: Routine Childhood Immunisation from Autumn 2006, UK

Age	Vaccine given	Mode of deliver (site)
2 months	DTaP/ IPV/ Hib (Pediacel)	Injection (thigh)
	PCV (Prevenar)	Injection (thigh)
3 months	DTaP/ IPV/ Hib (Pediacel)	Injection (thigh)
	Men C (Menjugate, Meningitec or Neisvac C)	Injection (thigh)
4 months	DTaP/ IPV/ Hib (Pediacel)	Injection (thigh)
	Men C (Menjugate, Meningitec or Neisvac C)	Injection (thigh, 2.5 cm from Pediacel injection)
	PCV (Prevenar)	Injection (opposite thigh)
12 months	Hib/ Men C (Menitorix)	Injection (thigh)
	MMR (Priorix or MMR II)	Injection (thigh)
13 months	PCV (Prevenar)	Injection (thigh)
3 years 4 months	dTaP/IPV (Repevax) or DTaP/IPV (Infanrix-IPV)	Injection (upper arm)
to 5 years	MMR (Priorix or MMR II)	Injection (upper arm)
13 to 18 years	Td/IPV (Revaxis)	Injection (upper arm)

Source: immunisation, NHS. Abbreviations can be found in page II.

Appendix H: Mid-2004 Population, UK



	Population	Proportion of total UK population
England	50,093,100	83.7%
Wales	2,952,200	4.9%
Scotland	5,078,400	8.5%
Northern Ireland	1,710,300	2.9%
UK	**59,834,300**	**100%**

Source: ONS.(190)

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