

TRENDS IN CHRONIC VIRAL HEPATITIS: NOTIFICATIONS, TREATMENT UPTAKE AND ADVANCED DISEASE BURDEN

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Abstract

Since the introduction of mandatory notification in the early 1990s, around 110,000 and 260,000 cases of hepatitis B and hepatitis C respectively, have been reported through public health surveillance mechanisms in Australia. The number of hepatitis B notifications is likely to be a considerable underestimation of the number of people living with chronic hepatitis B. Over the period 1998-2008, a small decrease in hepatitis B notifications (around 10%) and a more marked decrease in hepatitis C notifications (around 40%) has occurred, with the latter related to reductions in heroin supply. Rates of antiviral therapy remain low for both chronic hepatitis B (<3%) and chronic hepatitis C (<2%). Incidence of hepatocellular carcinoma has increased over the period 1990-2002, largely due to increasing contributions of hepatitis B virus and hepatitis C virus related hepatocellular carcinoma. Further increases in hepatocellular carcinoma incidence are projected, particularly if antiviral therapy uptake remains low. A combination of enhanced access to treatment programs and increased hepatocellular carcinoma screening among high risk people with chronic hepatitis B and chronic hepatitis C is required to limit the emerging epidemic of chronic viral hepatitis related hepatocellular carcinoma.

Globally, the major causation of hepatocellular carcinoma (HCC) is chronic hepatitis related to infection with hepatitis B virus (HBV) and hepatitis C virus (HCV).¹ More than 300 million people are estimated to be living with chronic HBV infection while 150 million are living with chronic HCV infection.² Despite the availability of a highly effective HBV vaccine for two decades, global chronic HBV prevalence will remain high for many years related to the late introduction of vaccine programs in many highly endemic countries and improved life expectancy. The long latency of HBV infection to advanced liver disease including HCC and low global HBV treatment uptake means that HCC incidence reduction will be even more protracted, possibly taking decades. The limited advances in HCV vaccine development, low HCV treatment uptake on a global level, and long latency from HCV infection to advanced liver disease mean that HCV related HCC will similarly be a major public health challenge for decades to come.

High level immigration from HBV endemic countries, particularly China and Vietnam, have increased HBV prevalence in Australia, with resultant increasing HBV related HCC incidence and projections of further increases over the next two decades.^{3,4} Escalating prevalence of injecting drug use in Australia from the 1980s has driven

the expanding HCV epidemic, with increases in HCV related HCC and further increases projected, similar to the situation with HBV.⁵

This review will cover available epidemiological data on HBV and HCV in Australia, including public health notifications, antiviral therapy uptake, and trends in HBV and HCV related HCC.

Unspecified/prevalent hepatitis B notifications

The low rate of progression to chronic HBV infection following incident infection among adolescents and adults, the major component of new transmission in Australia, means that incident infections make a limited contribution to the overall burden of HBV disease. The number and trends in unspecified or prevalent HBV notifications are therefore more informative of disease burden.

A diagnosis of hepatitis B has required mandatory notification in most Australian states and territories since the early 1990s. A total of 109,749 unspecified/prevalent hepatitis B infections were notified to the National Notifiable Diseases Surveillance System from 1990 to 2008 (table 1).⁶ Of note, there were no notifications from the Northern

Territory (NT) from 1990 until 2003. Notifications were also incomplete for other states and territories such as the Australian Capital Territory (ACT), South Australia (SA), and Victoria (VIC) until 1997. Thus, we report the data from 1998 to 2008.

Over the period 1998 to 2008, the highest number of hepatitis B notifications was from New South Wales (NSW, 47%), followed by VIC (26%), Queensland (QLD, 12%), Western Australia (WA, 7%), and SA (5%) (table 1 and figure 1). Hepatitis B notifications from the ACT and Tasmania (TAS) represent 1% or less each of the total notifications over the period.

Over the period 1998-2008, the number of hepatitis B notifications has fluctuated between 5000 and 8000 notifications per annum, with peaks in 2001 (7931) and 2008 (6948) (table 1). Over the last decade, there

was a net 10% increase in the number of hepatitis B notifications. Hepatitis B notifications were relatively stable for most states and territories, apart from NSW, which reflects the fluctuating national pattern.

Notifications for males were consistently higher than females, with a male to female ratio of approximately 1.1:1 to 1.3:1 (figure 2). The net increase in the number of notifications over the period was mainly attributable to the increase in the notifications for females; a 17% increase in notifications for females compared to only a 3% increase for males. The number of hepatitis B notifications was highest among people aged 30 to 39 years, followed by those aged 20 to 29 years and 40 to 49 years (figure 3). An increasing trend from 2006 to 2008 was seen among people aged 30 to 39 years, 50 to 59 years and those aged 60 and above.

Figure 1. National notifications of unspecified/prevalent hepatitis B by state and territory and year⁶

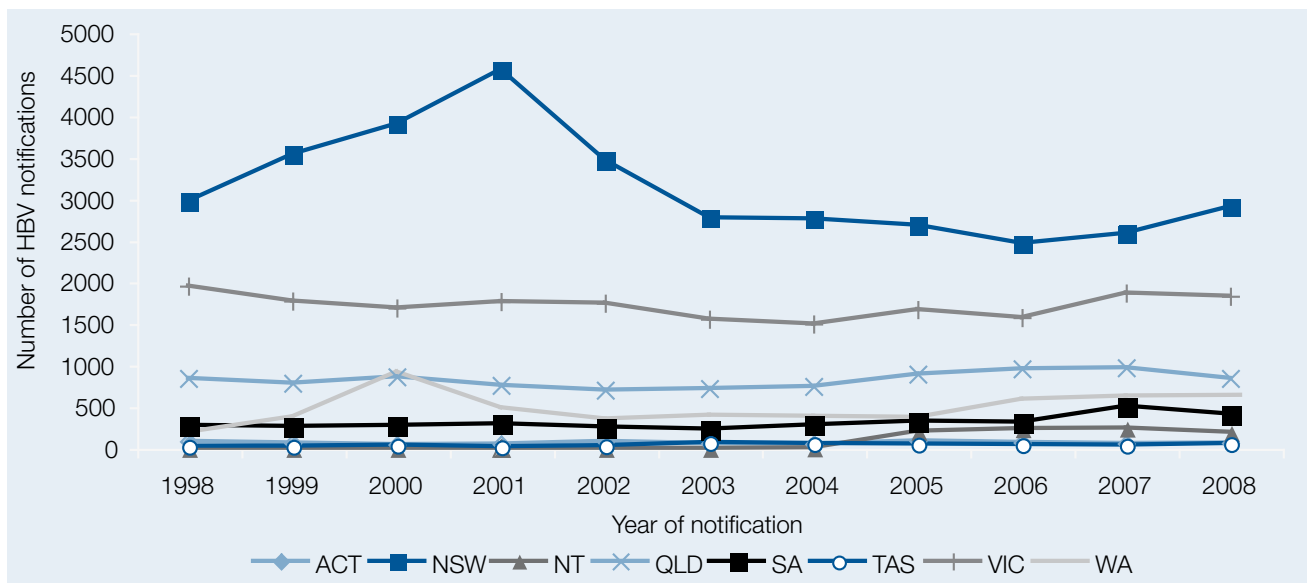


Figure 2. National notifications of unspecified/prevalent hepatitis B by gender and year⁶

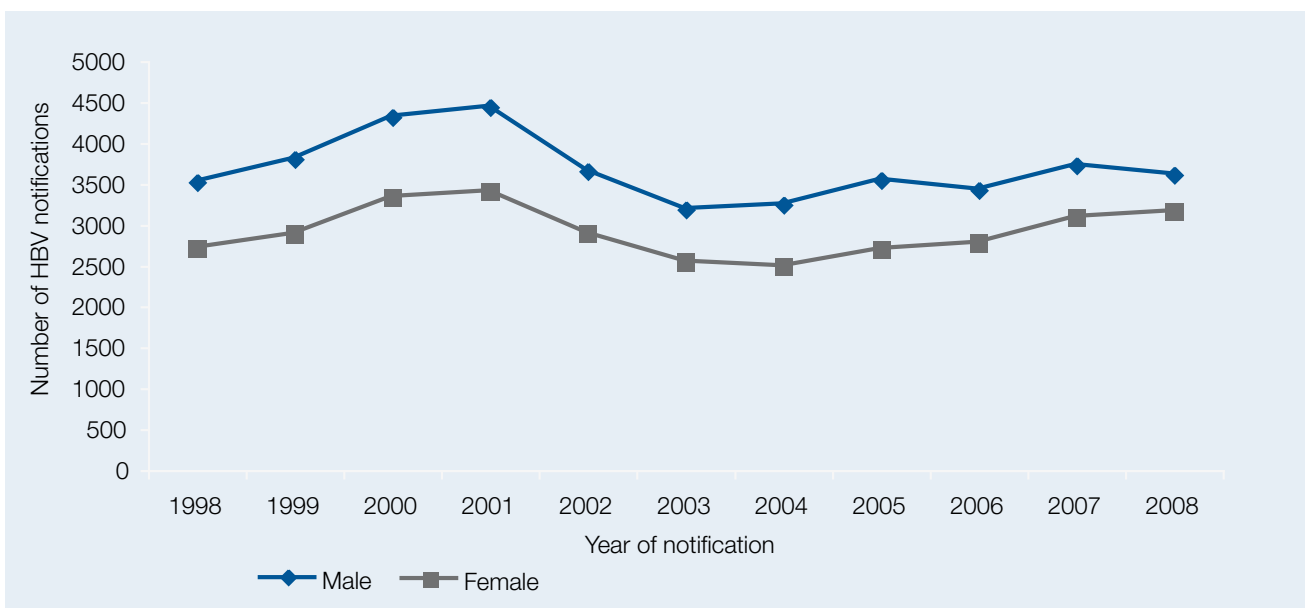


Table 1. Notifications of unspecified/prevalent hepatitis B by state and territory and year⁶

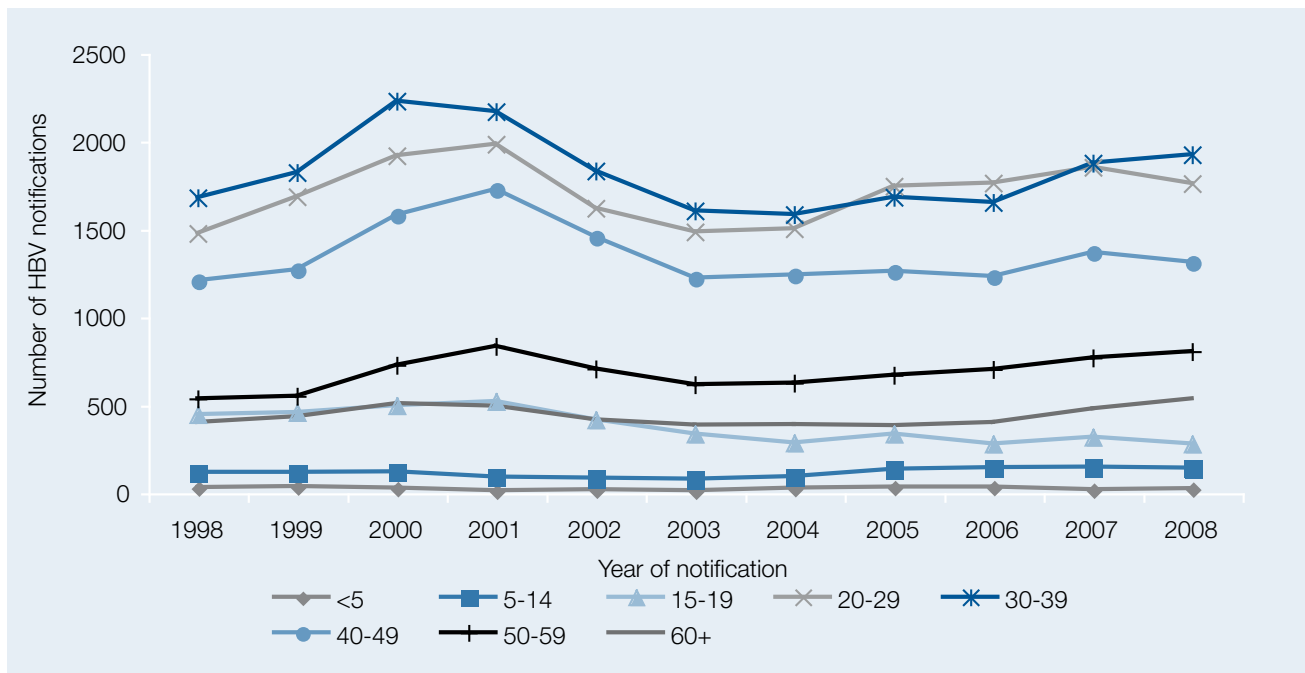
	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	Total
ACT	0	0	68	101	4	89	96	3	82	65	48	54	82	57	51	90	70	55	64	1079
NSW	4	582	2970	3445	3930	3985	3814	3165	2969	3535	3900	4559	3466	2771	2757	2685	2463	2589	2910	56499
NT	NN	NN	NN	NN	NN	NN	NN	NN	NN	NN	NN	NN	NN	NN	4	206	237	241	194	882
QLD	62	1483	1232	1241	986	867	913	835	840	786	859	758	702	720	744	892	959	967	843	16689
SA	0	0	0	0	0	0	321	317	274	260	276	293	257	232	282	325	315	506	413	4071
TAS	1	50	52	33	40	56	38	22	28	27	39	20	34	71	60	52	46	38	60	767
VIC	0	81	117	0	2	2	5	2321	1953	1770	1686	1762	1744	1556	1495	1667	1571	1870	1830	21432
WA	461	500	300	310	414	429	308	271	192	376	915	485	355	398	388	374	590	630	634	8330
Total	528	2696	4739	5130	5376	5428	5495	6934	6338	6819	7723	7931	6640	5805	5781	6291	6251	6896	6948	109749

NN, no notifications

Note: i) notifications for some state and territories such as ACT, SA, and VIC may be incomplete up to 1997.

ii) no notifications for NT until 2004.

iii) notifications for 2008 may be incomplete for all states and territories at the time of preparation of this manuscript.

Figure 3. Hepatitis B notifications (unspecified/prevalent) by age group and year⁶

Unspecified/prevalent hepatitis C notifications

The generally asymptomatic nature of incident HCV infection and lack of enhanced hepatitis C surveillance in most states and territories means that notified incident infections make a limited contribution to the overall burden of HCV disease. The number and trends in unspecified or prevalent HCV notifications are therefore more informative of disease burden.

A diagnosis of hepatitis C has required mandatory notification in most Australian states and territories since the early 1990s. A total of 259,861 unspecified/prevalent hepatitis C infections were notified to the National Notifiable Diseases Surveillance System from 1990 to 2008 (table 2). Notifications were incomplete for some states and territories such as the ACT and SA until 1994,

and NT and WA until 1992. For consistency, we report the data from 1998 to 2008.

Similar to hepatitis B notifications, the highest hepatitis C notifications over the period 1998 to 2008 were from NSW (41%), followed by VIC (25%), QLD (19%), WA (7%), and SA (4%) (table 2 and figure 4). Hepatitis C notifications from TAS and the NT represent 2% each and the ACT represents 1% of the total notifications over the period.

In contrast to the fluctuating pattern of hepatitis B, hepatitis C notifications peaked in 1999 (20,061) and have demonstrated a considerable decline since (table 2 and figure 4), although they have been relatively stable at just below 12,000 since 2005. There was a 30% decrease in the number of hepatitis C notifications from 1998 to 2008. Hepatitis C notifications declined in NSW, VIC and SA, but have been relatively stable in other states and territories.

Table 2. Notifications of unspecified/prevalent hepatitis C by state and territory and year

	1990	1991	1992	1993	1994	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	Total
ACT	0	1	98	242	3	325	266	12	288	276	212	211	224	240	209	159	177	191	195	3329
NSW	11	473	3754	5628	8005	7005	7481	7046	7255	8665	8141	8713	6639	5130	4846	4314	4330	4172	4516	106124
NT	0	10	96	218	293	312	222	286	232	187	191	212	201	217	260	255	266	227	221	3906
QLD	44	1489	2685	2641	2961	2784	2772	2825	2882	3019	3323	3097	2784	2582	2581	2661	2815	2714	2641	49300
SA	0	0	0	0	0	1061	1090	850	840	935	877	737	625	572	606	567	528	576	535	10399
TAS	2	27	110	157	301	226	262	195	255	280	298	316	320	345	285	213	259	255	316	4422
VIC	1	1669	1262	2658	3525	4515	4311	6496	4298	5723	4900	4611	3727	3469	2865	2833	2544	2614	2250	64271
WA	0	1	0	1105	1323	1122	1073	1025	1159	976	1577	1203	1020	1056	1014	954	1013	1197	1292	18110
Total	58	3670	8005	12649	16411	17350	17477	18735	17209	20061	19519	19100	15540	13611	12666	11956	11932	11946	11966	259861

Note: notifications for 2008 may be incomplete.

Figure 4. National notifications of unspecified/prevalent hepatitis C by state and territory and year⁶

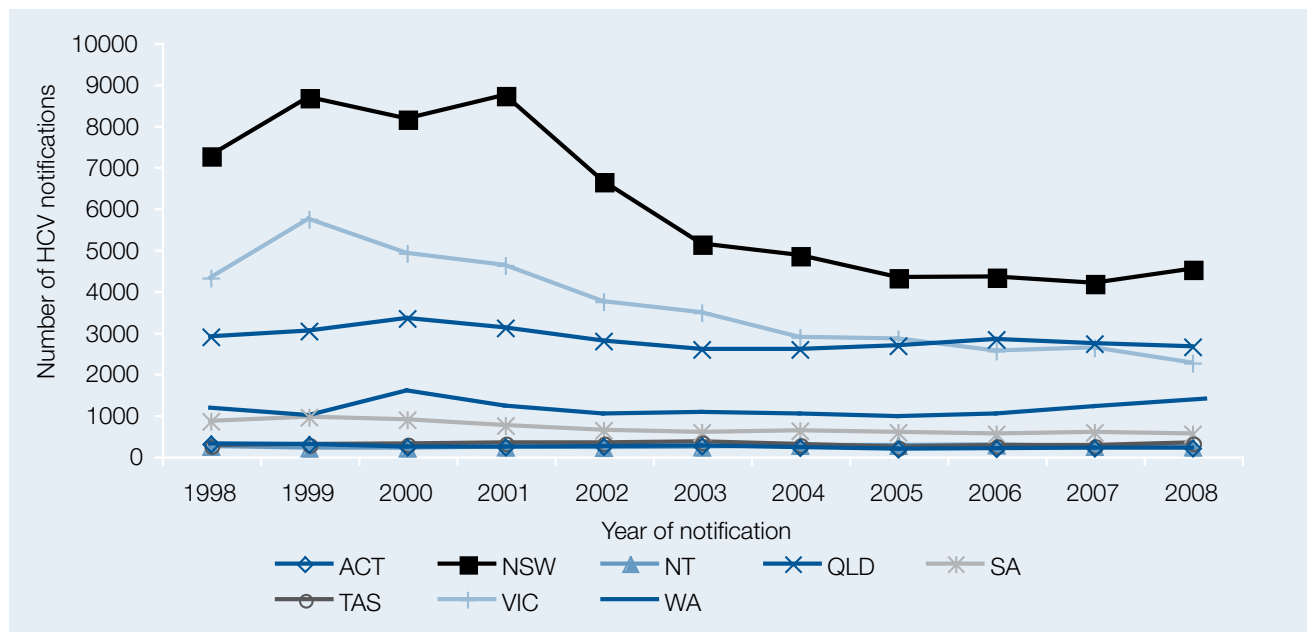
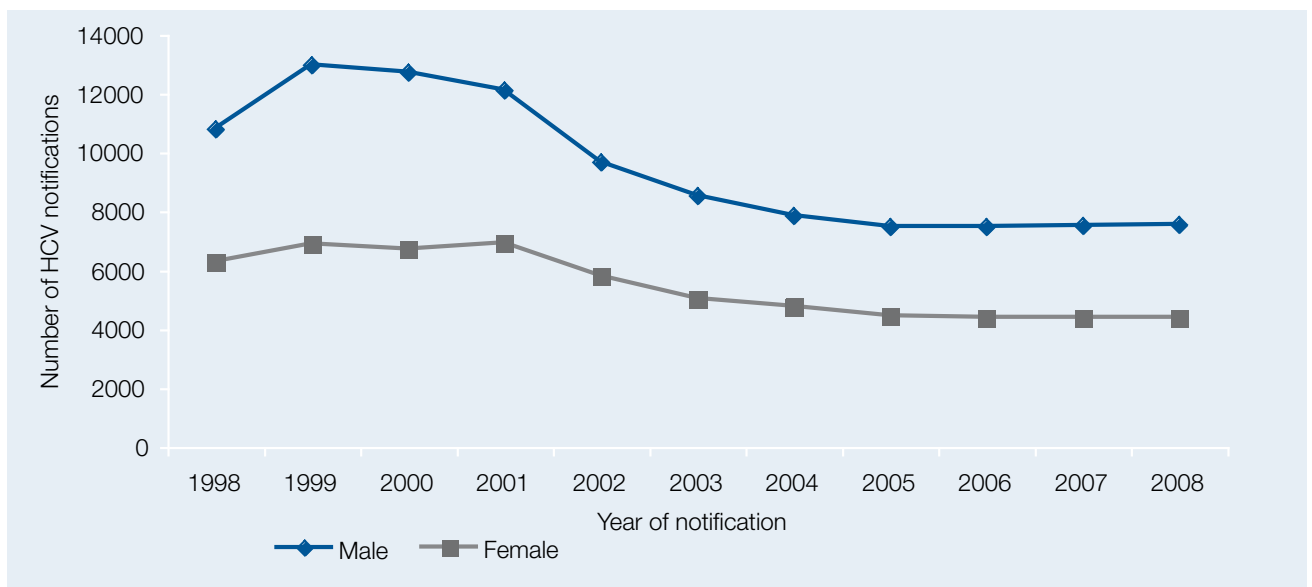


Figure 5. National notifications of unspecified/prevalent hepatitis C by gender and year⁶



Similar to hepatitis B, hepatitis C notifications for males were consistently higher than females, with a male to female ratio of approximately 1.7:1 (figure 5). The number of hepatitis C notifications was highest among people aged 20 to 29 years, 30 to 39 years and 40 to 49 years (figure 6). The number of hepatitis C notifications declined from 1998 to 2008 for all age groups except those

aged 50 to 59 years. The largest decline (57-72%) was seen in people aged less than 20 years. The number of notifications for people aged 20 to 39 were almost halved (40-44%) over the period.

Age distributions of both hepatitis B and C notifications were similar over the period 1998 to 2008 (figure 7), peaking in those aged 25-34 years and 25-39 years respectively.

Figure 6. Hepatitis C notifications (unspecified/prevalent) by age group and year⁶

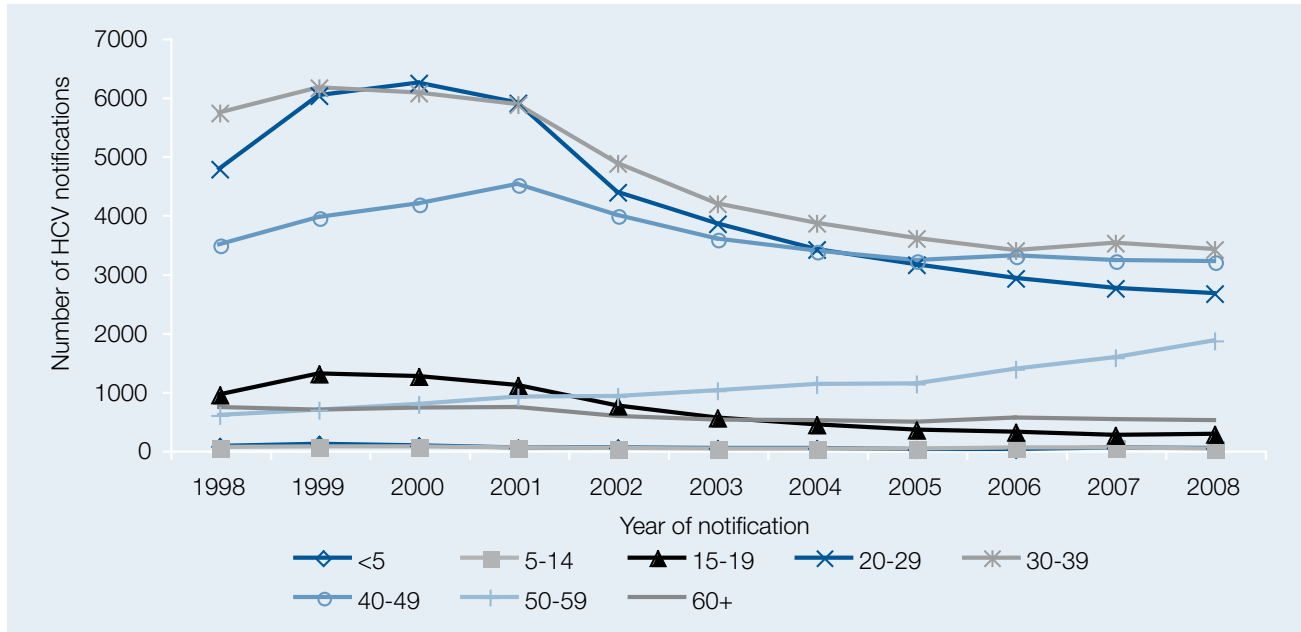
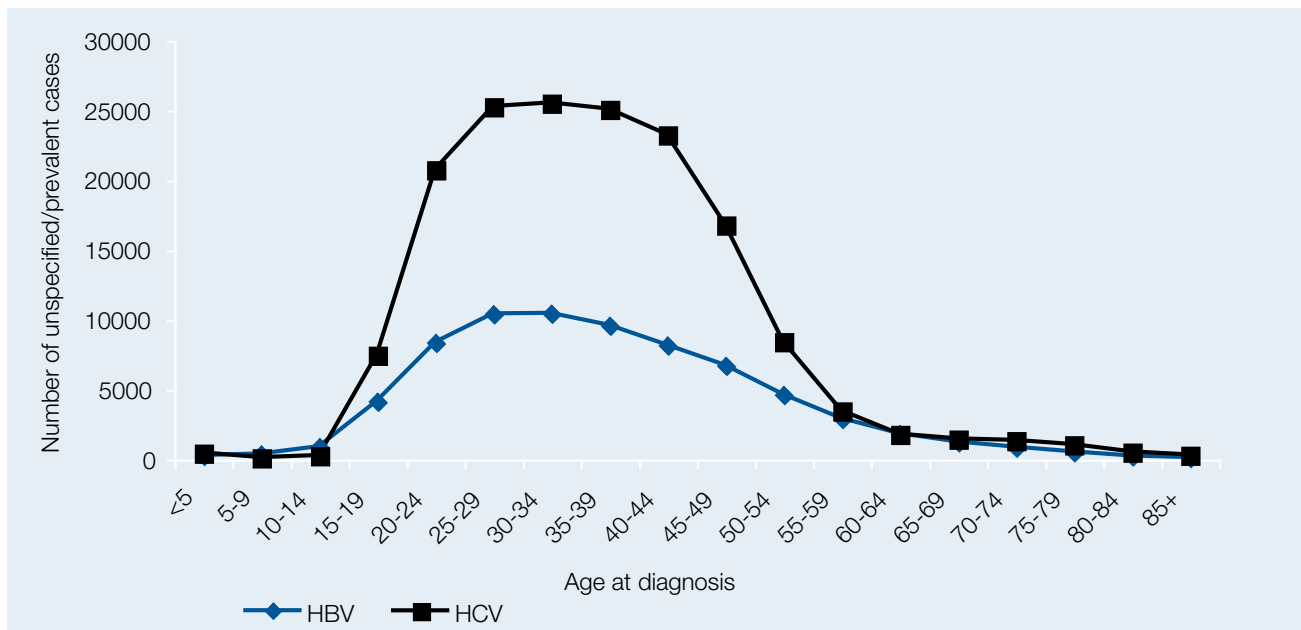


Figure 7. Age distribution of unspecified/prevalent hepatitis B and hepatitis C notifications, 1998-2008⁶



Trends in treatment uptake for hepatitis B

Antiviral therapy for chronic hepatitis B in Australia is provided largely through the Australian Government's Highly Specialised Drug S100 scheme, which provides highly subsidised treatment by approved specialist practitioners. The pattern of antiviral therapy uptake for chronic hepatitis B in Australia is shown in figure 8.⁷

The total number of prescriptions for chronic hepatitis B tripled from around 1000 at the beginning of 1999 to around 3000 at the end of 2007. Lamivudine was licensed in 1999 in many countries for treating selected patients with chronic hepatitis B. In Australia, lamivudine was the only agent available through the S100 scheme until 2004. The number of lamivudine prescriptions

through the S100 scheme increased from around 1000 at the beginning of 2003 to around 1400 at the end of 2007. Adefovir was included in the S100 scheme from the last quarter of 2004. The number of prescriptions for adefovir has doubled (from ~360 to ~720) since and contributed about a quarter of the total prescriptions in 2007. Entacavir was included in the S100 scheme from the last quarter of 2006, and its number of

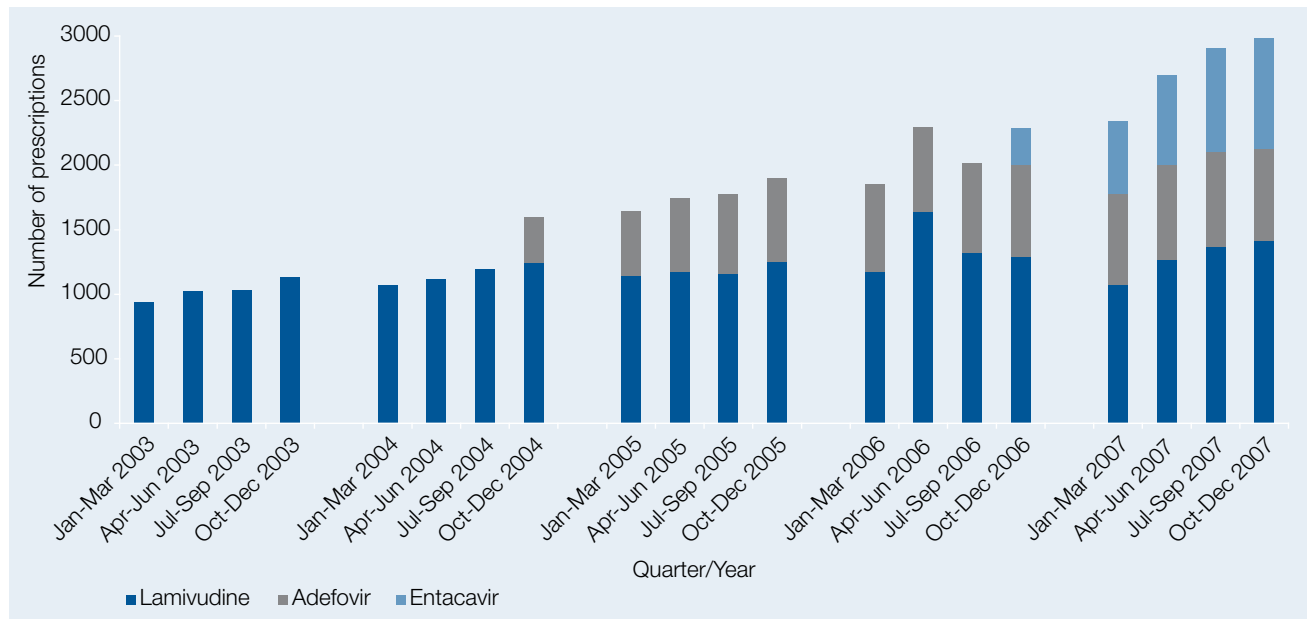
prescriptions has tripled from around 280 in 2006 to around 850 in 2007. Prior to 2008, these antiviral therapy agents were only approved as monotherapy for chronic hepatitis B. In 2008, approval was gained for combination lamivudine and adefovir therapy in the setting of lamivudine resistance. Pegylated interferon alfa-2a was also approved for chronic hepatitis B therapy in 2008.

Figure 8. Antiviral therapy for chronic hepatitis B, 2003 – 2007

Number of people dispensed drugs for hepatitis B infection through the Highly Specialised Drugs (S100) scheme, by year. Lamivudine: Number of person years of treatment with lamivudine 100mg estimated from the HSD Program Public Hospital Dispensed National Pack Number Report.

Adefovir included in S100 scheme from October 2004.

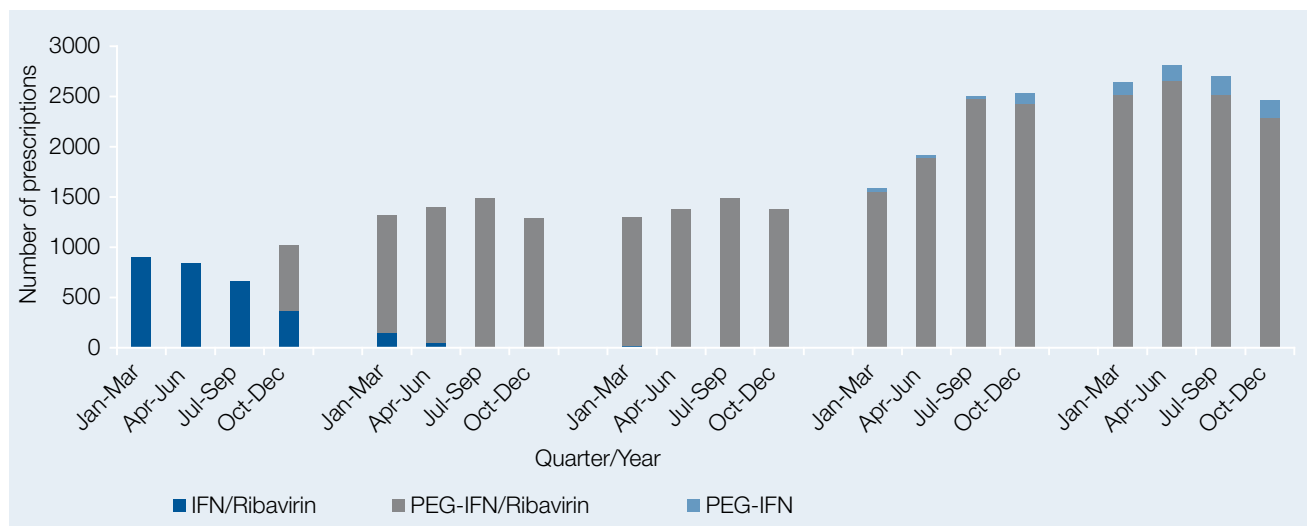
Entacavir included in S100 scheme from October 2006.



Source: Highly Specialised Drugs (S100) scheme; National Centre in HIV Epidemiology and Clinical Research (NCHECR) Annual Surveillance Report 2008.⁷

Figure 9. Interferon-based treatment for chronic hepatitis C, 2003 – 2007

Number of people dispensed drugs for hepatitis C infection through the Highly Specialised Drugs (S100) scheme. An estimated 1142, 1831, 1847, 2847 and 3539 people were receiving treatment throughout 2003 to 2007, respectively. From 1 April 2006, biopsy proven liver damage was no longer a requirement for treatment of hepatitis C infection. Pegylated interferon and ribavirin were included in the S100 scheme from 1 November 2003.



Source: Highly Specialised Drugs (S100) scheme; National Centre in HIV Epidemiology and Clinical Research (NCHECR) Annual Surveillance Report 2008.⁷

Trends in treatment uptake for hepatitis C

Antiviral therapy for chronic hepatitis C in Australia is also provided largely through the Australian Government's Highly Specialised Drug S100 scheme. The recent pattern of antiviral therapy for chronic hepatitis C is shown in figure 9.⁷ Hepatitis C treatment has improved in recent years with a substantial shift in the treatment from the standard interferon and ribavirin therapy prior to 2004 to pegylated interferon and ribavirin combination therapy in 2004. The number of prescriptions for hepatitis C through the S100 scheme has tripled from around 1000 in 2003 to around 3500 in 2007. The increase in the number of prescriptions for treatment of chronic hepatitis C started between the first and second quarters of 2006 coincided with the removal in April 2006 of the requirement for biopsy proven liver damage prior to treatment.

Trends in hepatitis B and hepatitis C related hepatocellular carcinoma in NSW

From 1990 through 2002, a total of 2727 primary liver cancer notifications were received by the NSW Central Cancer Registry.³ Of these, the majority (2072, 76%) were for HCC. The number of HCC notifications from 1990 to 2002 is shown in figure 10. Overall, 16% and 13% of HCC notifications were attributed to hepatitis B and C infections respectively, with higher proportions in more recent years. The majority (71%) of HCC notifications were unlinked. The number of hepatitis B related HCC notifications per annum increased by 48% from 27 in 1998 to 40 in 2002. The number of hepatitis C related HCC notifications per

annum increased to a lesser extent (by 28%) from 29 to 37, over the same period.

Age distribution of hepatitis B and C related HCC in NSW is shown in figure 11. Median age at HCC diagnosis was 58, 67, and 69 years for HBV and HCV linked and unlinked groups, respectively.³ Age distributions at HCC diagnosis for the HBV and HCV linked groups were bimodal, peaking in those aged 40-49 and 50-59 years and 45-49 and 70-74 years, respectively. In contrast, the age distribution of the unlinked HCC notifications was unimodal, with a peak in those aged 70-74 years.

Implications

Expanding epidemics of chronic hepatitis B and chronic hepatitis C in Australia are contributing to escalating rates of HCC. Total notifications of around 110,000 and 260,000 for hepatitis B and hepatitis C respectively, indicate the large burden of chronic viral hepatitis related liver disease. Low antiviral therapy uptake for both chronic hepatitis B and chronic hepatitis C suggest that therapeutic intervention is having a limited impact on HBV and HCV related HCC incidence.

Total notifications for unspecified/prevalent hepatitis B are the minimum estimate of chronic hepatitis B prevalence in Australia. Limited national reporting of hepatitis B diagnoses from some jurisdictions prior to 1997, in particular Victoria, would indicate that total diagnoses are considerably higher than the 110,000 notifications. The proportion of people with chronic hepatitis B in Australia who have undergone screening is difficult to

Figure 10. Distribution of hepatocellular carcinoma notifications by hepatitis linkage status over time, 1990-2002.³

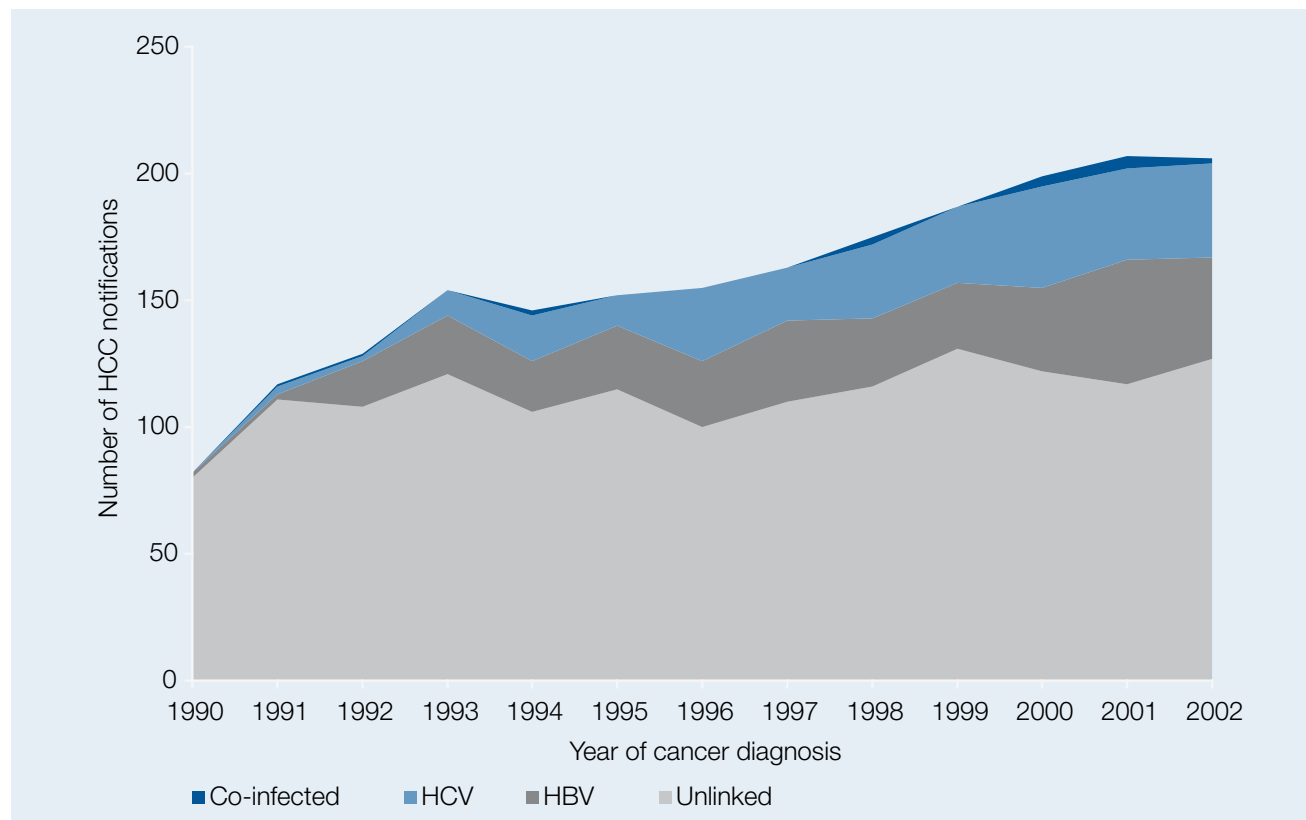
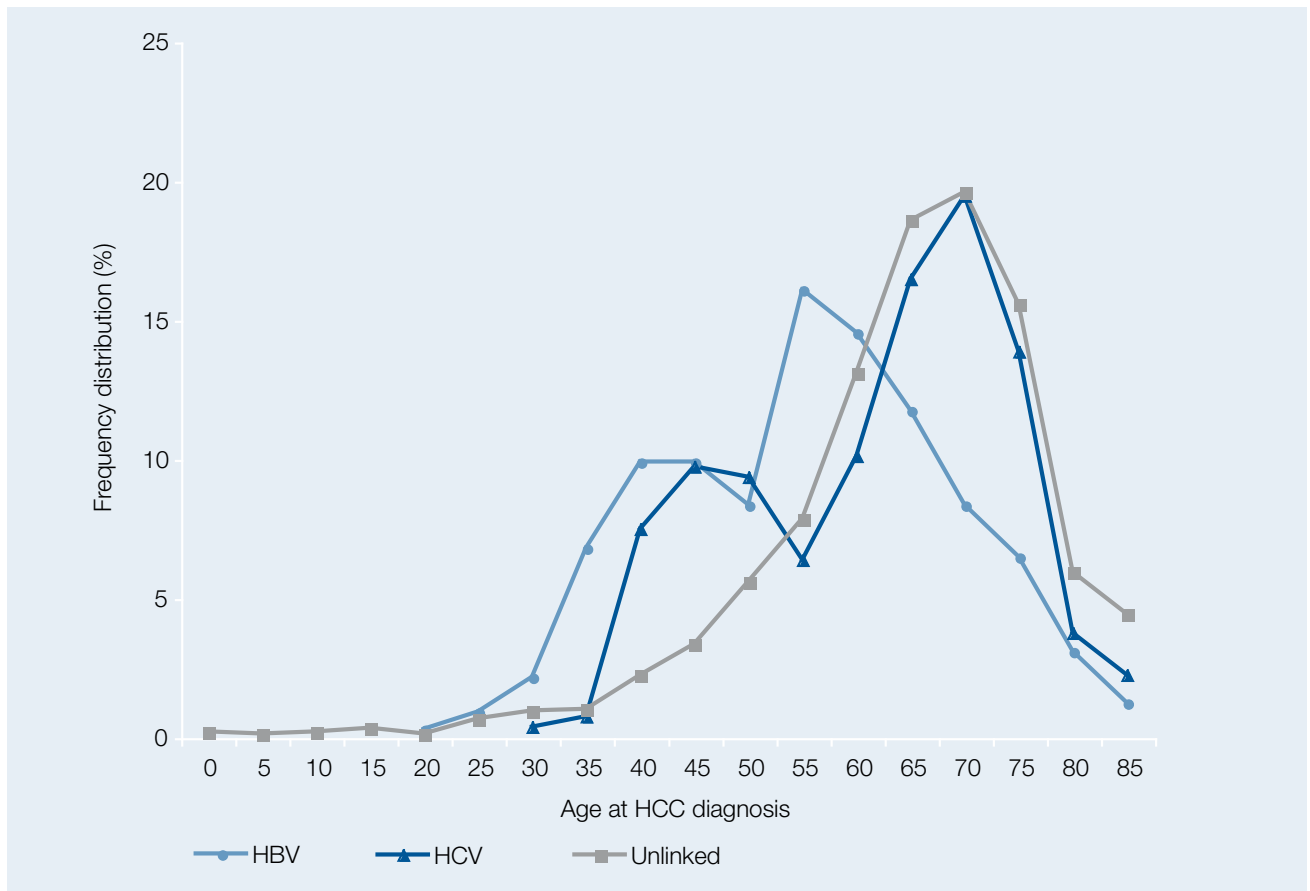


Figure 11. Age at diagnosis hepatocellular carcinoma by hepatitis linkage status, NSW, 1990-2002.³



estimate accurately, but is likely to be less than 75%. A more realistic estimate of the number of people living with chronic hepatitis B in Australia would be closer to 200,000. The major burden of chronic hepatitis B in Australia is among people born in the Asia-Pacific region, with estimates ranging from 50-70% and the two major sub-groups being those born in China and Vietnam.⁴ Other Australian population groups with relatively high prevalence of chronic hepatitis B are people born in sub-Saharan Africa and the Southern Mediterranean region, Indigenous Australians, men who have sex with men, and injecting drug users (IDU).⁸ There has been a small overall decline in hepatitis B notifications over the past decade, however the fluctuating levels of notifications is probably related to immigration flows from HBV endemic countries rather than a reflection of HBV transmission within Australia.

Hepatitis B notifications are based on detection of HBsAg which generally indicates evidence of chronic hepatitis B. In contrast, hepatitis C notifications are based on detection of anti-HCV antibody which does not indicate chronic hepatitis C. An estimated 25% of people with HCV infection will undergo spontaneous HCV clearance and not progress to chronic hepatitis C.⁹ Further, when screening is undertaken in low risk populations, false positive anti-HCV antibody results are common. Thus, total notifications of unspecified/prevalent hepatitis C of around 260,000 are likely to reflect chronic hepatitis C cases of closer to 200,000. A proportion of people with chronic hepatitis C in Australia, possibly 25%, will not

have been screened, therefore the estimate of people living with chronic hepatitis C in Australia may be around 250,000. The major population groups in Australia with chronic hepatitis C are IDU (former and current) and people born in high prevalence countries such as Egypt, Italy and South-East Asia.¹⁰ The considerable decline in hepatitis C notifications since 2000 has been attributed to reductions in heroin supply, the so-called 'heroin drought', from the same period.⁵ The marked decline in notifications among younger age groups indicates this trend is likely to reflect true declines in HCV transmission. In contrast, the increasing number of notifications in the 50-59 year age group may reflect increased screening of both former IDU and people from high prevalence countries.

Data from the NSW linkage study clearly indicates the increasing contribution of hepatitis B and hepatitis C to HCC incidence.³ The bimodal age distribution of both HBV and HCV related HCC is particularly interesting. In the case of HCV related HCC, it is likely to reflect two distinct hepatitis C epidemics: a large epidemic among former and current IDU, with many now infected for more than 20 years and therefore at risk of having progressed to advanced liver disease, and; a smaller epidemic among people born in high prevalence countries, but with many of this group being infected for more than 30 years and the longer duration of infection contributing to a relatively greater burden of HCC. Previously published data from the NSW linkage study indicates that a large proportion of the older HCV related HCC cases are among people born overseas.³ Given the continued rising incidence of

HCC since the end of the linkage study period in 2002, it is highly likely that numbers of HBV and HCV related HCC are continuing to increase. Recent modelling of hepatitis B among people born in Asia-Pacific countries⁴ and the hepatitis C estimates and projections working group report⁵ support this upward trend. Of greater concern are the further increases in HBV and HCV related HCC over the next two decades that are projected, particularly if therapeutic uptake remains low.

The number of people currently on antiviral therapy for chronic hepatitis B through the S100 scheme is around 3000.⁷ Although additional prescriptions are provided through private hospitals and practitioners and through clinical trial protocols, the total number of people receiving therapy is likely to be less than 5000. This would represent less than 3% of the estimated number of people with chronic hepatitis B in Australia. Although a large proportion of people with chronic hepatitis B do not require antiviral therapy, particularly younger people in the immunotolerant phase of infection, the rate of treatment uptake is extremely low and unlikely to be having a major impact on HCC incidence. Two major strategies are required to limit the projected increase in HBV related HCC over coming years: increased antiviral therapy uptake, particularly for those older than 40 years with high HBV viral load, and; HCC screening for those with established or suspected cirrhosis.

Rates of antiviral therapy uptake for chronic hepatitis C are similarly low, at around 3500 per year and again representing a small proportion (less than 2%) of the estimated number of people with chronic hepatitis C in Australia.⁷ This level of therapeutic intervention is likely to have a limited impact on HCC incidence. Although antiviral therapy uptake through the S100 scheme has increased from around 2000 per year since the removal of mandatory pre-treatment liver biopsy staging, the simultaneous broadening of treatment criteria (previously evidence of significant liver damage was required) means that many people with early liver disease are likely to be receiving therapy. The limited risk of advanced liver disease over the next one to two decades in this group means that recent therapy uptake increases may have a relatively limited impact on HCC incidence. Similar to chronic hepatitis B, a combination of further increases in

antiviral therapy uptake, particularly among people with significant liver fibrosis, and HCC screening among people with proven or suspected cirrhosis is required to limit projected increases in HCC incidence.

In conclusion, expanding epidemics of chronic hepatitis B and chronic hepatitis C in Australia are contributing to the rapidly escalating incidence of HCC. Considerable investment in expanded treatment and care programs, along with more widespread implementation of HCC screening, is required to reduce the anticipated further increases in HCC incidence.

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