



Modelling of the potential for outbreaks of Measles in Wales

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Details of Report

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Authors:

Dr Christopher Johnson – Head of Vaccine Preventable Disease Programme (VPDP)

Dr Simon Cottrell – Senior Principal Epidemiologist, VPDP.

Malorie Perry – Epidemiological Scientist (Advanced), VPDP

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Executive summary

Measles poses a significant risk in Wales and in the UK with cases reported across Wales. Public Health Wales has reported cases in several areas including Swansea, Cardiff and Newport. In a number of cases these have led to small, localised outbreaks. However, whilst these are small, they have a significant impact on local services and healthcare in particular.

This report presents a model which aims to investigate the risk of large outbreaks across Wales. Based on earlier models which have looked at risk on large geographical areas across England, this approach uses similar techniques to investigate the variation at a small area level. The model is not predictive and does not demonstrate that a large outbreak will occur but highlights which areas could sustain sufficient levels of community transmission that are required for larger prolonged outbreaks to develop.

The output of the model highlights that most areas in Wales should not sustain significant levels of community transmission. As a result, importations of infection should burn out relatively quickly without significant risk of widespread community transmission becoming established. However, some areas could sustain significant community transmission resulting in large outbreaks occurring. The highest risk of sustained transmission leading to large outbreaks is predicted in the 18-24 age group, and that this manifests itself particularly in university towns (Cardiff, Swansea, Bangor, Aberystwyth).

Uncertainty in the modelling parameters has been explored via sensitivity analysis to explore different assumptions on vaccine effectiveness and vaccine uptake. This shows that uncertainty in vaccine uptake has the biggest impact on areas with lower vaccination rates where the model predicts the largest outbreaks could occur. Alternately, uncertainty on vaccine effectiveness has the highest impact on the overall risk across Wales and impacts especially in areas with high vaccine uptake.

The report makes 11 recommendations to address issues on prevention, response and further development of the model to support policy and practice in Wales.

1. Background and purpose

During 2024, a large vaccination campaign was conducted across Wales focusing on improving recorded uptake of two doses of MMR vaccine in school aged children (Welsh Government, 2024). As a result over 1,500 and 1,000 first doses were delivered to primary school and secondary school aged children in Wales respectively (Public Health Wales, 2024). Furthermore, over 2,000 and 1,000 second doses were delivered to primary school and secondary school aged children in Wales respectively.

However, at the end of the exercise 200 primary schools and 25 secondary schools still had uptake recorded in the child health system of less than 90% for two doses of MMR which makes them at increased susceptibility for outbreaks of disease (Public Health Wales, 2024).

This report describes the development of a model which seeks to identify areas in Wales where there are sufficient susceptible individuals to sustain significant outbreaks of measles in order to support targeted action. Furthermore, the model developed will underpin further work to estimate how the risk of outbreaks will change over time based on current patterns of uptake. This report does not



provide predictions of the likely size of outbreaks across Wales or where they are likely to occur most often, but rather a means to help identify areas of high susceptibility where large outbreaks could be sustained in order to prioritise risk in local areas. Factors outside this report, such as community links with countries where measles is endemic would need to be considered to estimate where importation events and seeding of outbreaks is most likely to occur.

2. Methods

This section sets out the development of the model and the parameters and assumptions that underpin the outputs.

2.1. Reproductive number

The basic reproductive number for a disease (R_0) is defined as the average number of secondary cases directly generated by one case of infection in a population where all individuals are susceptible. The effective reproductive number (R_e) is the average number of secondary cases in a population made up of susceptible and non-susceptible individuals (Aronson, et al., 2020).

In areas where $R_e < 1$, each case will lead to an average of less than 1 secondary case and therefore any potential clusters following importations of infection would be expected to burn out quickly even in the absence of any other effective control measures. The smaller the value of R_e the quicker on average clusters will burn out (Aronson, et al., 2020). However, outbreaks can still occur in these areas due to heterogeneity in the population with regards to immunity and population mixing. To achieve effective elimination, the WHO recommended targets that achieved a value of R_e within an area below 0.7 (Ramsey, 1997).

In areas where $R_e > 1$, there is the potential for exponential growth of cases as each new case will on average result in more than 1 secondary case and therefore in the absence of other effective control measures a major outbreak could be sustained. The larger the value of R_e the faster an will develop with each generation of transmission leading to increased growth. Areas where $R_e > 1$ are considered at risk for a major outbreak.

The effective reproductive number (R_e) for each area was calculated using the output of the Next Generation Matrix (Equation 1), in a similar approach to that outlined by Choi *et al* (Choi, et al., 2008) and MacIntyre *et al* (MacIntyre, et al., 2003). This approach takes into account the proportion of susceptible individuals and the differences in inter- and intra- group attack rates between age groups which allows for the effects of heterogeneity in age related transmission to be taken into account within a population (the likelihood of a case transmitting to any susceptible individual is not constant as the degree of interaction between individuals in different age groups is not constant).

Within the matrix R_{0ij} is the basic reproductive number for that transmission event (average number of secondary cases that would occur in the i^{th} age group (row) resulting from a single case in the j^{th} age group (column). So, in a completely susceptible population a case in the 11-17 age group will result in an average 1.8 secondary cases in the 5-10 year age group)).

Equation 1 – Next Generation Matrix for measles in a fully susceptible population

$$NGM = \begin{matrix} & \begin{matrix} 0-4 & 5-10 & 11-17 & 18-24 & 25+ \end{matrix} \\ \begin{pmatrix} 1.92 & 0.38 & 0.38 & 0.38 & 0.38 \\ 0.47 & 4.98 & 1.80 & 0.47 & 0.47 \\ 0.38 & 1.80 & 7.48 & 0.47 & 0.47 \\ 0.47 & 0.47 & 0.47 & 8.72 & 0.47 \\ 5.22 & 5.22 & 5.22 & 5.22 & 5.22 \end{pmatrix} & \begin{matrix} 0-4 \\ 5-10 \\ 11-17 \\ 18-24 \\ 25+ \end{matrix} \end{matrix}$$

As not all individuals in each age group are susceptible then the effective reproduction number for each cell (R_{eij}) in the matrix is calculated by multiplying the basic reproductive number for that cell (R_{0ij}) with the proportion of susceptible individuals in that age group (x_i). The overall value of R_e for the area is then calculated as the leading eigenvalue for the next generation matrix.

Equation 2 – Next generation matrix for a population where only a proportion of the population in age group i (x_i) are susceptible

$$R_e = \begin{pmatrix} 1.92x_{0-4} & 0.38x_{0-4} & 0.38x_{0-4} & 0.38x_{0-4} & 0.38x_{0-4} \\ 0.47x_{5-10} & 4.98x_{5-10} & 1.80x_{5-10} & 0.47x_{5-10} & 0.47x_{5-10} \\ 0.38x_{11-17} & 1.80x_{11-17} & 7.48x_{11-17} & 0.47x_{11-17} & 0.47x_{11-17} \\ 0.47x_{18-24} & 0.47x_{18-24} & 0.47x_{18-24} & 8.72x_{18-24} & 0.47x_{18-24} \\ 5.22x_{25+} & 5.22x_{25+} & 5.22x_{25+} & 5.22x_{25+} & 5.22x_{25+} \end{pmatrix}$$

Calculations to determine the leading eigenvalue were performed in R.

2.2. Susceptible Population

One of the key parameters in the model was the proportion of the population that were susceptible to measles (x_i) in each age group. This is based on a combination of previous exposure to infection and vaccination coverage. For the model used, the population was broken up into five separate age cohorts.

For the younger age groups susceptibility is based on vaccination coverage as recorded in CYPRIS, the data from which is extracted to create the National Community Child Health Database (NCCHD) which is used as the national population vaccination register.

2.2.1. Children aged under 18

Data on the number of children and number of MMR vaccines recorded in single year age bands between 0 and 17 years of age were extracted from the NCCHD and assigned to the appropriate MSOA based on the current recorded address of the child. The age band of the child was based on age as of 1st June 2024.

2.2.2. 18-24 years old

Data on young adults aged 18-24 years old is based on archived NCCHD data and GP records held within the SAIL database. To comply with information governance restrictions the percentage of individuals with either 1 or 2 MMR within the 18-24 age group recorded as living in each MSOA. This uptake percentage was applied to mid-year population estimates for 2023 (Office for National Statistics, 2024) in order to estimate the number of susceptible and protected individuals in the

population.

2.2.3. Over 25 years old

The population aged over 25 was divided into two broad categories. Those born between 1970 and 1999 (aged 25-54) were assumed to have a susceptibility of 5% whilst those born when measles was still endemic in the UK (before 1970) were assumed to have a susceptibility of 2%. This iteration of the model assumes that immunity is permanent once achieved. Recent research has shown that there is a potentially important waning of vaccine induced immunity over time (Robert, et al., 2024). This means that a fixed model is likely to underestimate susceptibility especially in older age groups with vaccine induced immunity.

2.2.4. Vaccine Effectiveness

It is recognised that vaccine effectiveness is not 100%, and therefore even after vaccination a small proportion of the population will remain susceptible. A recent Cochrane review (Di Pietrantonj, et al., 2020) found that vaccine effectiveness in preventing measles was 95% [CI 87%-98%] for one dose and 96% [CI 72%-99%] for two doses. The effectiveness of preventing cases among household or other close contacts was 81% [CI 11-96%] and 85% [CI 77-99%] after two doses.

In line with the original methodology by Choi *et al*, the base model assumes that one dose of MMR vaccine is 90% effective, and two doses are 99% effective against infection from measles. All those under the age of 25 with no recorded doses of vaccine are considered to be susceptible (Choi, et al., 2008). However, the impact of vaccine effectiveness is examined in the sensitivity analysis.

2.3. Major outbreak size

Although outbreaks can occur in areas where $R_e < 1$, they should be self-limiting in size. Using a similar approach to Choi *et al* (Choi, *et al*, 2008), the potential size of any major outbreak for any area where R is modelled to exceed 1 is calculated by doubling the number of individuals required to reduce R_e to 1. This was modeled 2 two steps.

Step 1 – reduce R_{eij} to <1 for each cell within the NGM

The number of cases required in age group i within area b to reduce R_{eij} to 1 (n_{bi}) is calculated for a population of size p_{bi} where a proportion of those (x_{bi}) are already protected against infection with basic reproductive number for R_{0ij} (Equation 3). The value of n_{bi} is then rounded to the next whole integer to ensure that every value of R_{eij} in the matrix is marginally less than 1.

Equation 3 - Number of cases required in population b to reduce R_e for age group i to 1

$$n_{bi} = p_{bi} \left(x_{bi} - \frac{1}{R_{0ij}} \right)$$

Step 2 – reduce R_e to <1 for whole matrix

A matrix containing any values close to 1 will still result in an overall R_e over >1 . Therefore, having

reduced all the cells in the NGM to marginally less than 1, the value of the resolved matrix is reduced to <1 by iteratively removing an additional susceptible individual from each age groups in the population, and repeating this until the leading eigenvalue of the matrix is <1. The number of additional cases required to reduce the value of the whole matrix to <1 is equal to the number of repetitions required of step 2 (n_{bit}) before the whole matrix resolves to a value <1.

The maximum number in a large outbreak in area b (N_{Outb}) is then calculated by adding all these values together and doubling it (Equation 4).

Equation 4 - Number of cases in a large outbreak

$$N_{outb} = 2(\sum_{i=0-4}^{25+} n_{bi} + n_{bit})$$

This calculation was repeated 1,000 times, and the average taken as the maximum outbreak size for each area. This approach reduces the variation in outbreak size resulting from the random removal of susceptible individuals and produces a central estimate with confidence intervals.

2.4. Sensitivity Analysis

2.4.1. Underestimation of vaccine uptake

Evidence from studies comparing GP practice and child health data has shown evidence of under-reporting within CYPRIS (Perry, et al., 2023), and that the extent of that under-reporting increases with age. The underestimation of uptake has the potential to be significantly larger in the 18-24 year age group due to the increased movement of people in and out of areas, especially within the larger university towns and metropolitan areas, reducing the accuracy of records.

In order to look at the potential impact of this on the model, sensitivity analysis was undertaken where the model assuming a percentage of those with no recorded vaccine have had one vaccine, and a percentage of those thought to have one vaccine have had two vaccines (Table 1). The impact of this can be seen for different age groups in high, moderate or low uptake examples (Table 2) .

Table 1 - Age group specific correction factor applied in recorded vaccine uptake during sensitivity analysis

Age Group	Underreporting factor
0-4	7.5%
5-10	15%
11-15	22.5%
18-24	35%

2.4.2. Vaccine Effectiveness

In order to look at the impact of uncertainty around vaccine effectiveness the sensitivity analysis looks at the impact of using the different Cochrane estimates of vaccine effectiveness (95% for one dose, 96% for two doses) on the model. (Di Pietrantonj, et al., 2020).

Table 2 - Corrected vaccination uptake for examples of a high, moderate and low vaccination uptake examples

Age Group	High Uptake 95% MMR1 90% MMR2		Moderate uptake 85% MMR1 75% MMR2		Low uptake 70% MMR1 50% MMR2	
	Modelled MMR1	Modelled MMR 2	Modelled MMR 1	Modelled MMR 2	Modelled MMR 1	Modelled MMR 2
0-4	95.4%	90.4%	86.1%	75.8%	72.3%	51.7%
5-10	95.8%	90.9%	87.3%	76.8%	74.5%	53.7%
11-15	96.1%	91.4%	88.4%	78.0%	76.8%	56.0%
18-24	96.8%	92.4%	90.3%	80.3%	80.5%	60.7%

2.4.3. Uncontrolled outbreak size

In order to look the impact of the methodology on the potential outbreak size an alternative method was also used. This method was based on a study which suggested that there was a bifurcated linear relationship between the susceptible population and outbreak size in highly vaccinated populations (Wallinga, et al., 2005). When the size of the total susceptible population exceeds 4.6%, major outbreaks can form which can have 1.6 cases for every additional susceptible individual. This was used to look at impact of different methods on predicted outbreak size.

3. Results

3.1. Baseline output – Geographical variation in risk

The baseline model estimates that most MSOAs (n=291) in Wales would not sustain significant outbreaks following the importation of a case. However 72 have a value of R_e which does not meet the WHO target for elimination of <0.7 . Moreover, there are 47 additional MSOAs where the modelled value to R_e is greater than 1 (Table 3, Figure 1-2)

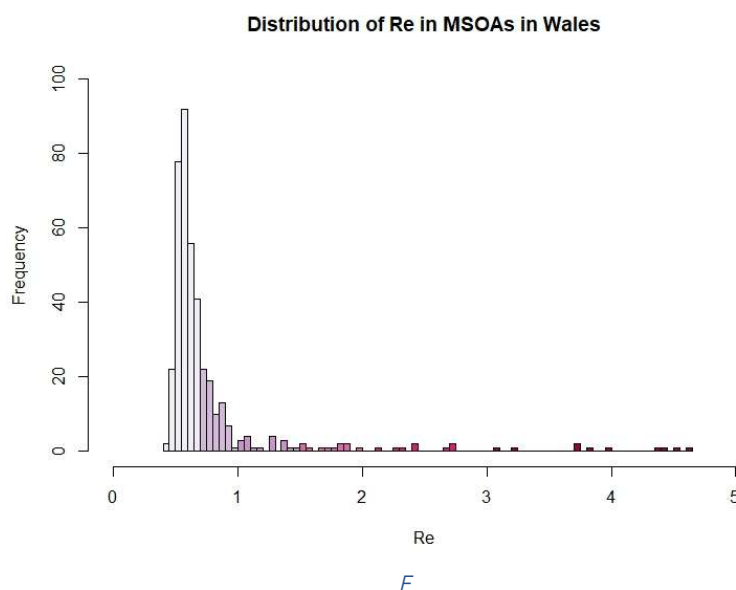
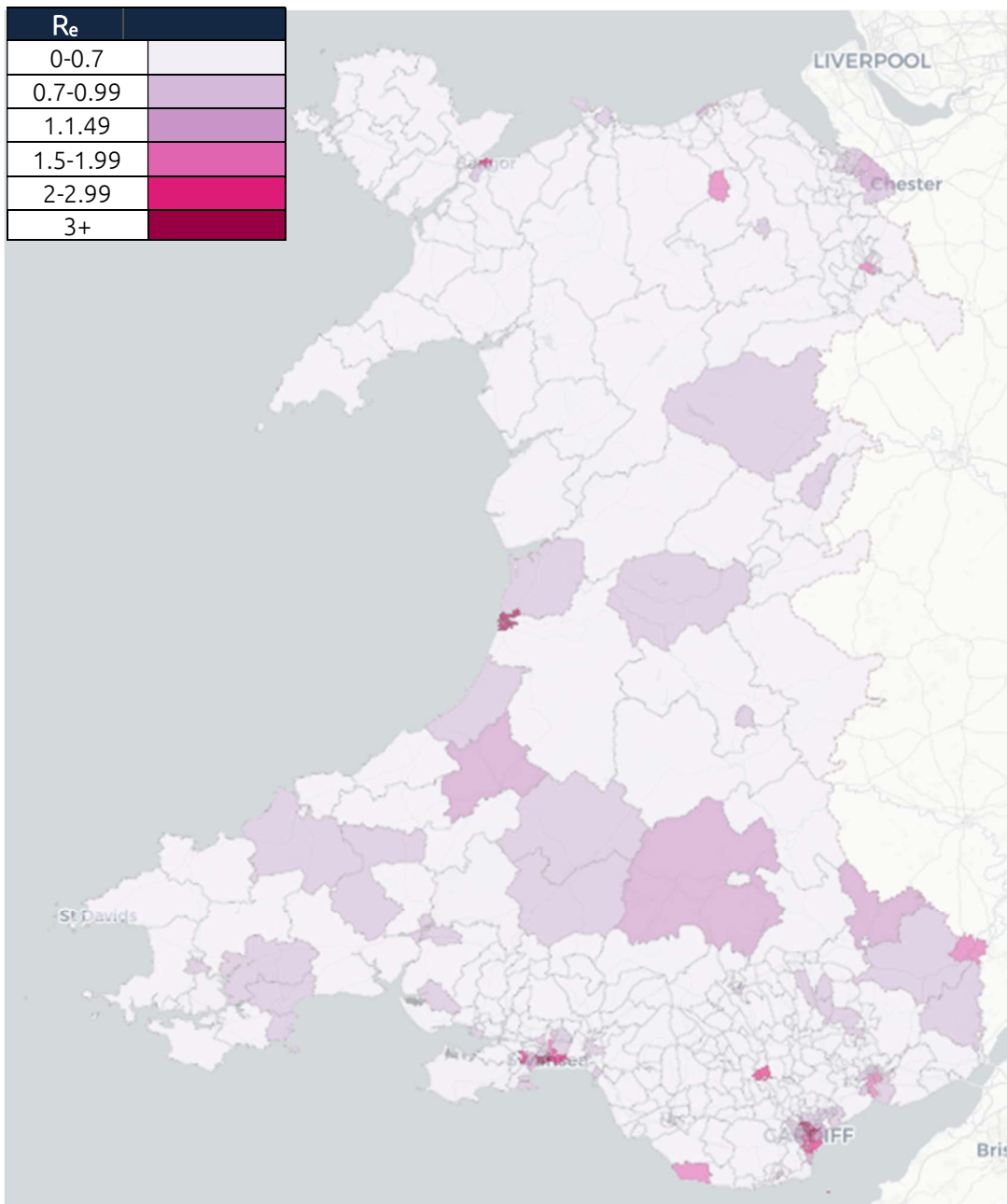


Figure 1 – Histogram showing the distribution of values of R_e for all MSOAs in Wales

Table 3 – Number of MSOAs in each health board area with $R_e < 1$ and major outbreaks could take hold, or where R_e is < 1 and either above or below the WHO threshold for effective elimination.

Health Board	Number of MSOAs				
	$R_e < 0.7$	$R_e = 0.7-1$	$R_e = 1-2$	$R_e = 2-3$	$R_e = 3-5$
Aneurin Bevan	55	15	7		
Betsi Cadwaladr	77	10	6	1	
Cardiff and Vale	30	13	11	4	5
Cwm Taff Morgannwg	54	2		1	
Hywel Dda	32	15	1		2
Powys	13	5	1		
Swansea Bay	30	12	3	2	3
Wales	291	72	29	8	10

Figure 2 - Map of all MSOA in Wales showing the modelled value of R_e (where $R_e > 1$ a major outbreak could be sustained)



3.2. Local Health Board Analyses

3.2.1. Aneurin Bevan University Health Board Area

There were seven MSOAs in the Aneurin Bevan University Health Board area with an $R_e > 1$, five in Newport and two in Monmouthshire (Table 4 - MSOAs with $R_e > 1$ in Aneurin Bevan University Health Board with estimated major outbreak size and main contributing groups, Figure 3). A further 15 have values of R_e above the WHO threshold for effective elimination.

Table 4 - MSOAs with $R_e > 1$ in Aneurin Bevan University Health Board with estimated major outbreak size and main contributing groups

County	MSOA Name	Overall R_e	Mean estimate of major outbreak size	Age groups where $R_e > 0.7$	R_e	Vaccine Uptake	
						MMR1	MMR2
Monmouthshire	Monmouth & Wyesham	1.59	376	11-17 18-24	1.49 1.24	81.2% 87%	77.9% 84%
	Abergavenny South & Crucorney	1.07	45	11-17	0.91	89.0%	85.6%
Newport	Stow Hill	1.85	440	18-24	1.54	84%	75%
				11-17	1.47	81.9%	74.3%
				5-10	1.12	79%	71.5%
				0-4	0.73	-	-
	Victoria & Somerton	1.76	565	18-24	1.70	82%	76%
				11-17 5-10	0.99 0.8	88.3% 85.4%	80.6% 78.3%
Pillgwenlly & Docks	1.75	550	18-24	1.68	82%	77%	
			11-17	1.08	86.9%	81.5%	
			5-10	0.74	86.6%	85.4%	
Maendy	1.52	319	18-24	1.43	85%	79%	
			11-17	1.08	86.8%	82.1%	
			5-10	0.73	86.9%	80.1%	
St Julians & Barnardtown	1.26	127	18-24	1.17	88%	83%	
			11-17	0.79	90.6%	87.0%	

The biggest driver of risk in the model for the Aneurin Bevan UHB area is young adults (18-24 years old) in the central area of Newport, followed by 11-17 year olds, especially Stow Hill and Monmouth & Wyesham.

The five higher risk MSOAs in Newport are all contiguous with each other, and can therefore be considered to be a single area in which transmission can take hold. By combining the areas within the model it is possible to consider this as an area with a population of 43,400 where there are 4,220 susceptible individuals, and a case imported into that area could, without appropriate control, initiate an outbreak of up to 2,220 across the area.

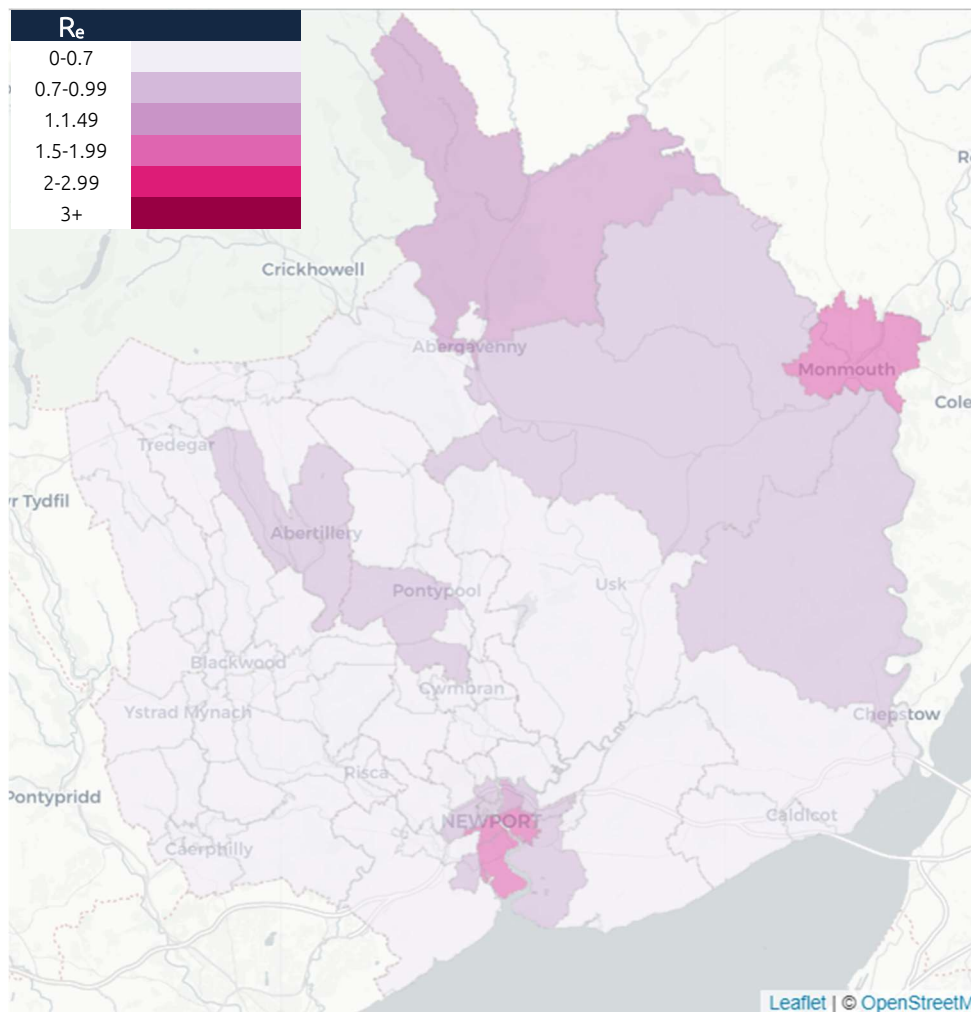


Figure 3 - Map of all MSOA in the Aneurin Bevan University Health Board area showing the modelled value of R_e (where $R_e > 1$ a major outbreak could be sustained)

3.2.2. Betsi Cadwaladr University Health Board

There were seven MSOAs in the Betsi Cadwaladr University Health Board area with an $R_e > 1$, one in Gwynedd, two in Flintshire, two in Denbighshire and two in Wrexham (Table 5 - MSOAs with $R_e > 1$ in Betsi Cadwaladr University Health Board with estimated major outbreak size and main contributing groups, Figure 4 - Map of all MSOA in the Betsi Cadwaladr University Health Board area showing the modelled value of R_e (where $R_e > 1$ a major outbreak could be sustained). A further 10, have values of R_e above the WHO threshold for effective elimination .

The biggest driver of risk in the model for the BCUHB area is 18-24 year olds in Wrexham, Bangor, Rhyl and Shotton. However, the highest risk outside Bangor is associated with susceptible 11-17 year olds particularly in the Denbigh area.

There are 2 neighboring clusters each containing 2 MSOAs with $R_e > 1$ in in BCUHB. One in Wrexham and the other in Flintshire. The Flintshire cluster has a population of 9,960 where there are 780 susceptible individuals. The Wrexham cluster has a population of 10,250 where there are 750 susceptible individuals. In both areas an imported case into that area could, without appropriate control, lead to a outbreak size of approx. 180 across the area.

Table 5 - MSOAs with $R_e > 1$ in Betsi Cadwaladr University Health Board with estimated major outbreak size and main contributing groups

County	MSOA Name	Overall R_e	Mean estimate of major outbreak size	Age groups where $R_e > 0.7$	R_e	Vaccine Uptake	
						MMR1	MMR2
Gwynedd	Bangor City	2.23	1829	18-24	2.16	76%	71%
				11-17	1.53	80.9%	75.4%
				5-10	0.83	84.6%	81.2%
Denbighshire	Denbigh West	1.82	228	11-17	1.72	77.9%	77.3%
	Rhyl North	1.04	33	18-24	1.41	85%	82%
Flintshire	Shotton & Garden City	1.44	135	18-24	1.41	85%	82%
	Queensferry & Sandycroft	1.29	62	18-24	1.23	87%	84%
Wrexham	Wrexham West	1.53	126	18-24	1.49	84%	81%
	Hermitage & Whitegate	1.27	80	11-17	0.81	90.4%	87.0%
Wrexham	Hermitage & Whitegate	1.27	80	18-24	1.23	87%	84%

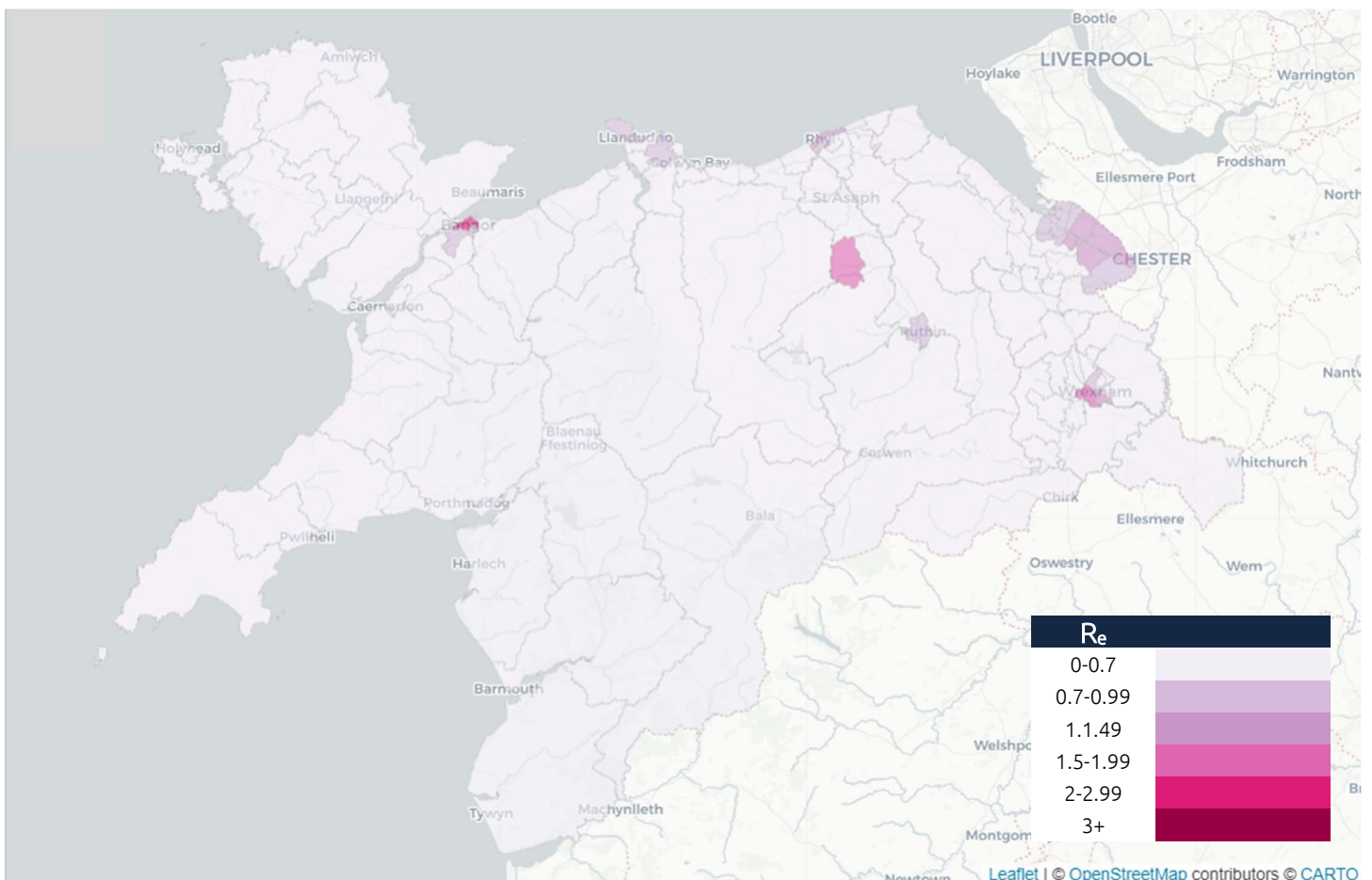


Figure 4 - Map of all MSOA in the Betsi Cadwaladr University Health Board area showing the modelled value of R_e (where $R_e > 1$ a major outbreak could be sustained)

3.2.3. Cardiff and the Vale University Health Board

There were 19 MSOAs in the Cardiff and the Vale University Health Board area with an $R_e > 1$, accounting for nearly half of all high risk areas in Wales within the model. The majority of these risk areas are located in Cardiff. The highest risk area in Wales is also located in Cardiff (Cathays South and Bute Park) where transmission could be sustained in three age groups driving a very significant outbreak (Figure 5, Table 6).

In addition, there were a further 13 MSOAs where R_e exceeds the WHO threshold for effective elimination of Measles.

Table 6 - MSOAs with $R_e > 1$ in Cardiff and the Vale University Health Board with estimated major outbreak size and main contributing groups

County	MSOA Name	Overall R_e	Mean estimate of major outbreak size	Age groups where $R_e > 0.7$	R_e	Vaccine Uptake	
						MMR1	MMR2
Cardiff	Cathays South & Bute Park	4.29	7253	18-24	4.22	52%	42%
				11-17	2.52	68.0%	57.4%
				5-10	1.12	79.7%	64.9%
	Cathays North	3.74	4347	18-24	3.71	58%	49%
				11-17	1.41	82.9%	72.1%
	Gabalfa	3.91	3285	18-24	3.89	56%	46%
				11-17	0.81	90.5%	85.8%
	Adamsdown	3.68	2075	18-24	3.64	59%	51%
				11-17	1.46	82.1%	73.5%
	Plasnewydd	3.14	1912	18-24	3.11	65%	56%
				11-17	1.09	86.8%	81.9%
	Roath	2.7	1121	18-24	2.68	70%	65%
				11-17	0.87	89.7%	84.3%
	Butetown	2.4	701	18-24	2.35	74%	69%
				11-17	1.28	84.3%	77.3%
	Cardiff Bay	2.66	668	18-24	2.60	71%	65%
				11-17	1.77	77.8%	69.4%
	Grangetown North	2.41	437	18-24	2.38	74%	68%
	South Riverside	1.97	260	18-24	1.93	79%	75%
11-17				0.82	90.5%	84.5%	
Splott	1.82	144	18-24	1.79	81%	73%	
Grangetown South	1.38	102	18-24	1.33	86%	82%	
Tremorfa & Pengam	1.4	97	18-24	1.36	86%	80%	
Birchgrove	1.43	94	18-24	1.41	85%	79%	
Pontcanna	1.36	75	18-24	1.32	86%	81%	
Pen-y-lan South	1.19	60	18-24	1.15	88%	85%	
Canton	1.02	20	18-24	0.98	90%	87%	
The Vale of Glamorgan	Llantwit Major	1.67	132	18-24	1.66	82%	80%
	Penarth	1.11	38	18-24	1.07	89%	86%

The 17 MSOAs in Cardiff and one in the Vale of Glamorgan (Penarth) are all contiguous with each other, and can therefore be considered to a single area in which transmission can take hold. By combining the areas it is possible to consider this as an area with a population of 159,000 where there are over 21,000 susceptible individuals, and a case imported into that area could, without appropriate control, could result in a maximum outbreak size of 22,700. A very large outbreak in the Cardiff area, is very likely to result in a significant number of cases across the whole South East Wales area, even if transmission was not sustained in significant amounts in the surrounding areas.

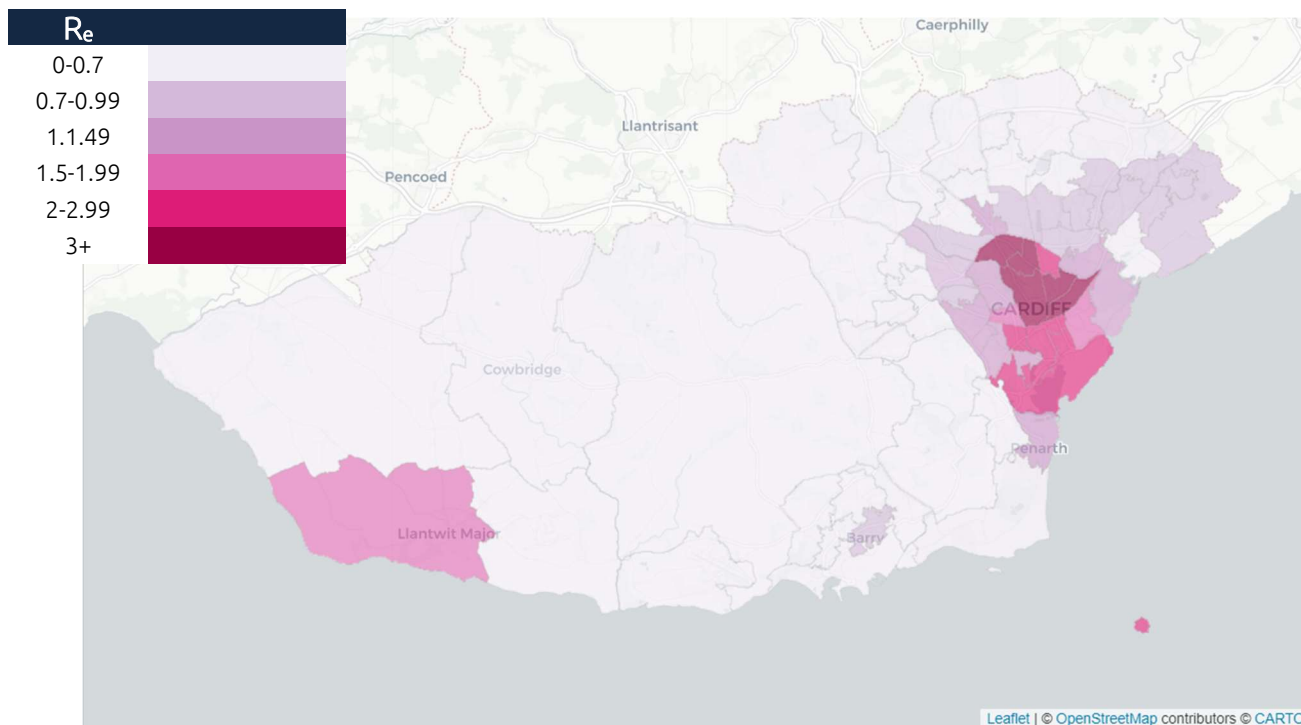


Figure 5 - Map of all MSOA in the Cardiff and the Vale University Health Board area showing the modelled value of R_e (where $R_e > 1$ a major outbreak could be sustained)

3.2.4. Cwm Taff Morgannwg University Health Board

There was only one MSOA in the Cwm Taff Morgannwg UHB area with an $R_e > 1$, located within Rhondda Cynon Taff, covering the areas of Treforest (Figure 6, Table 7). In addition, there were a further 2 MSOAs where R_e exceeds the WHO threshold for effective elimination of Measles .

Table 7 - MSOAs with $R_e > 1$ in Cwm Taff Morgannwg University Health Board with estimated major outbreak size and main contributing groups

County	MSOA Name	Overall R_e	Mean estimate of major outbreak size	Age groups where $R_e > 0.7$	R_e	Vaccine Uptake	
						MMR1	MMR2
Rhondda Cynon Taf	Treforest	2.62	1156	18-24	2.60	71%	66%

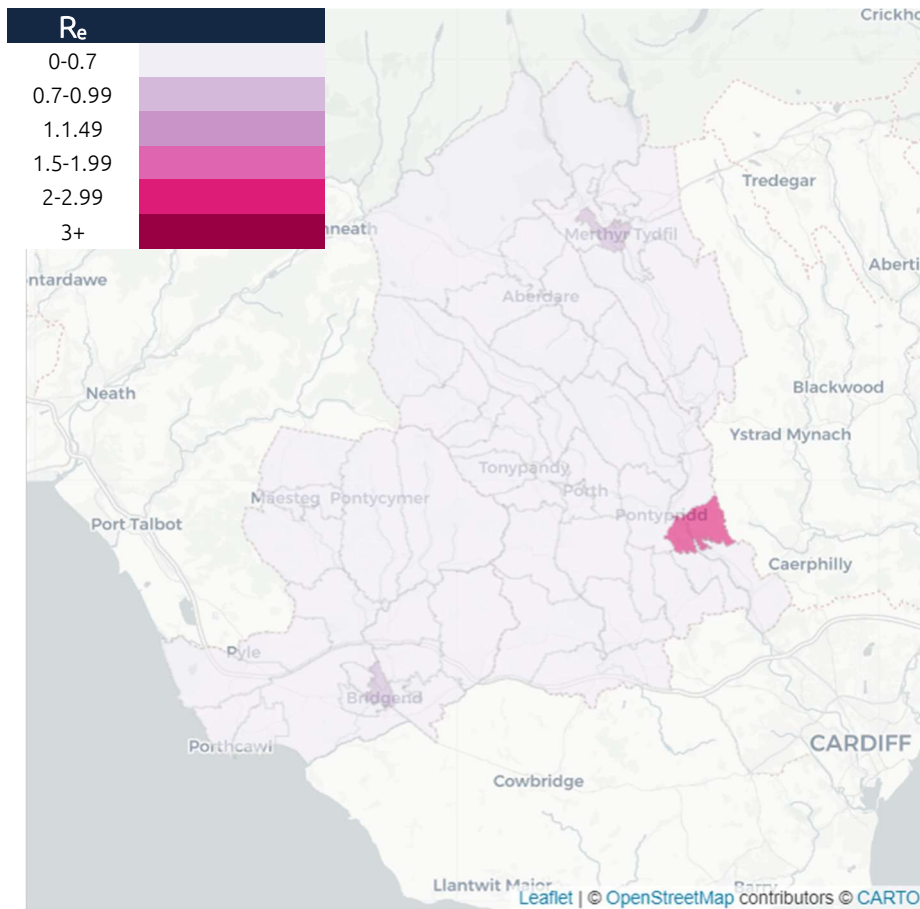


Figure 6 - Map of all MSOA in the Cwm Taf Morgannwg University Health Board area showing the modelled value of R_e (where $R_e > 1$ a major outbreak could be sustained)

3.2.5. Hywel Dda University Health Board

There were three MSOAs in the Hywel Dda University Health Board area with an $R_e > 1$, all in Ceredigion. Two of the three MSOAs are located in Aberystwyth, whereas the third is associated with the Lampeter area. Transmission risk within the model in these areas are all associated with young adults aged 18-24 (Table 8, Figure 7 - Map of all MSOA in the Hywel Dda University Health Board area showing the modelled value of R_e (where $R_e > 1$ a major outbreak could be sustained)). In addition, there were a further 15 MSOAs where R_e exceeds the WHO threshold for effective elimination of Measles.

Table 8 - MSOAs with $R_e > 1$ in Hywel Dda University Health Board with estimated major outbreak size and main contributing groups

County	MSOA Name	Overall R_e	Mean estimate of major outbreak size	Age groups where $R_e > 0.7$	R_e	Vaccine Uptake	
						MMR1	MMR2
Ceredigion	Lampeter & Llanfihangel Ystrad	1.04	50	18-24	0.99	90%	83%
	Aberystwyth South	3.05	780	18-24	3.03	66%	64%
	Aberystwyth North	4.51	4025	18-24	4.49	49%	46%

The two MSOAs in Aberystwyth are both contiguous with each other, and can therefore be considered to a single area in which transmission can take hold. This area has a population of 12,200 where there are 3,300 susceptible individuals, and a case imported into that area could, without appropriate control, to reach a maximum outbreak size of 4,700 across the wider area.

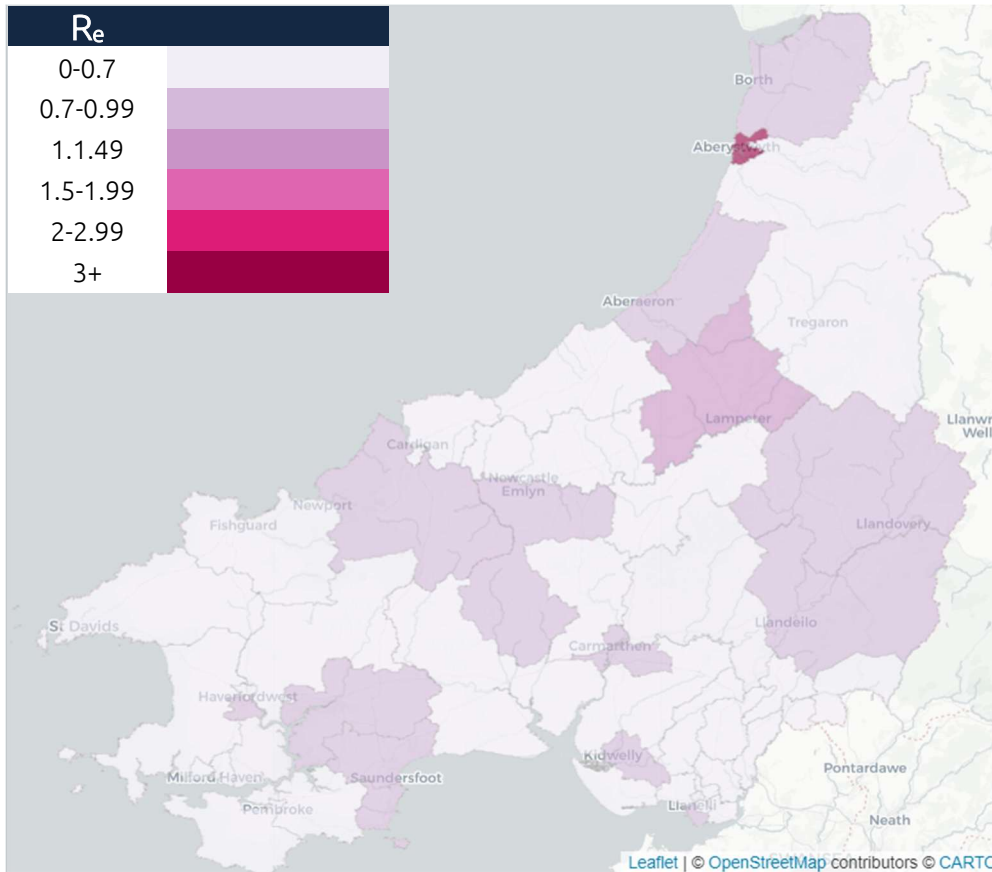


Figure 7 - Map of all MSOA in the Hywel Dda University Health Board area showing the modelled value of R_e (where $R_e > 1$ a major outbreak could be sustained)

3.2.6. Powys Teaching Health Board

There was only 1 MSOA in the Powys THB area with an $R_e > 1$, located close to Brecon (Figure 8, Table 9), and a further five where R_e exceeds the WHO threshold.

Table 9 - MSOAs with $R_e > 1$ in Powys Teaching Health Board with estimated major outbreak size and main contributing groups

County	MSOA Name	Overall R_e	Mean estimate of major outbreak size	Age groups where $R_e > 0.7$	R_e	Vaccine Uptake	
						MMR1	MMR2
Powys	Sennybridge & Talybont-on-Usk	1.06	23	18-24	1.04	89%	89%

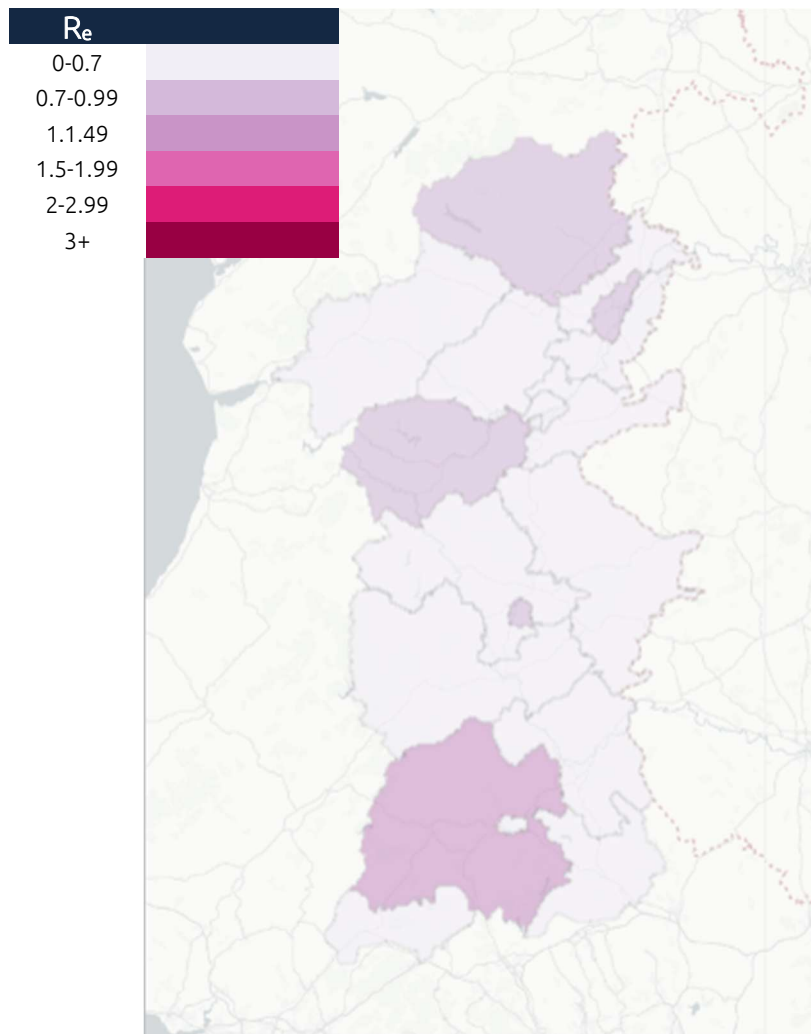


Figure 8 - Map of all MSOA in the Powys Teaching Health Board area showing the modelled value of R_e (where $R_e > 1$ a major outbreak could be sustained)

3.2.7. Swansea Bay University Health Board Area

There were eight MSOAs in the Swansea Bay University Health Board area with an $R_e > 1$ all in Swansea (Table 10, Figure 9), and a further 12 which have an R_e value greater than the WHO target for elimination .

All eight MSOAs in Swansea are all contiguous with each other, and can therefore be considered to a single area in which transmission can take hold. By combining the areas it is possible to consider this as an area with a population of 47,800 where there are 8,260 susceptible individuals, and a case imported into that area could, without appropriate control, be expected to lead to a maximum outbreak size of 9,890 cases

Table 10 - MSOAs with $Re > 1$ in Swansea Bay Health Board with estimated major outbreak size and main contributing groups

County	MSOA Name	Overall Re	Mean estimate of major outbreak size	Age groups where $Re > 0.7$	Re	Vaccine Uptake	
						MMR1	MMR2
Swansea	Sketty	1.25	142	18-24	1.04	87%	82%
	Brynmill	4.61	4394	18-24	4.57	48%	43%
				11-17	1.15	86.4%	76.5%
				5-10	1.06	80.2%	72.8%
	Central Swansea	4.37	2348	18-24	4.32	51%	45%
				11-17	2.15	86.4%	76.5%
				5-10	1.08	80.2%	72.8%
	Uplands	3.66	2165	18-24	3.63	59%	53%
11-17				1.10	86.9%	79.8%	
5-10				0.92	82.9%	72.8%	
Killay	2.11	293	18-24	2.08	77%	72%	
Ty-coch	1.12	47	18-24	1.07	89%	85%	
St Thomas	2.30	346	18-24	2.27	75%	70%	
Landore	1.88	348	18-24	1.84	80%	74%	

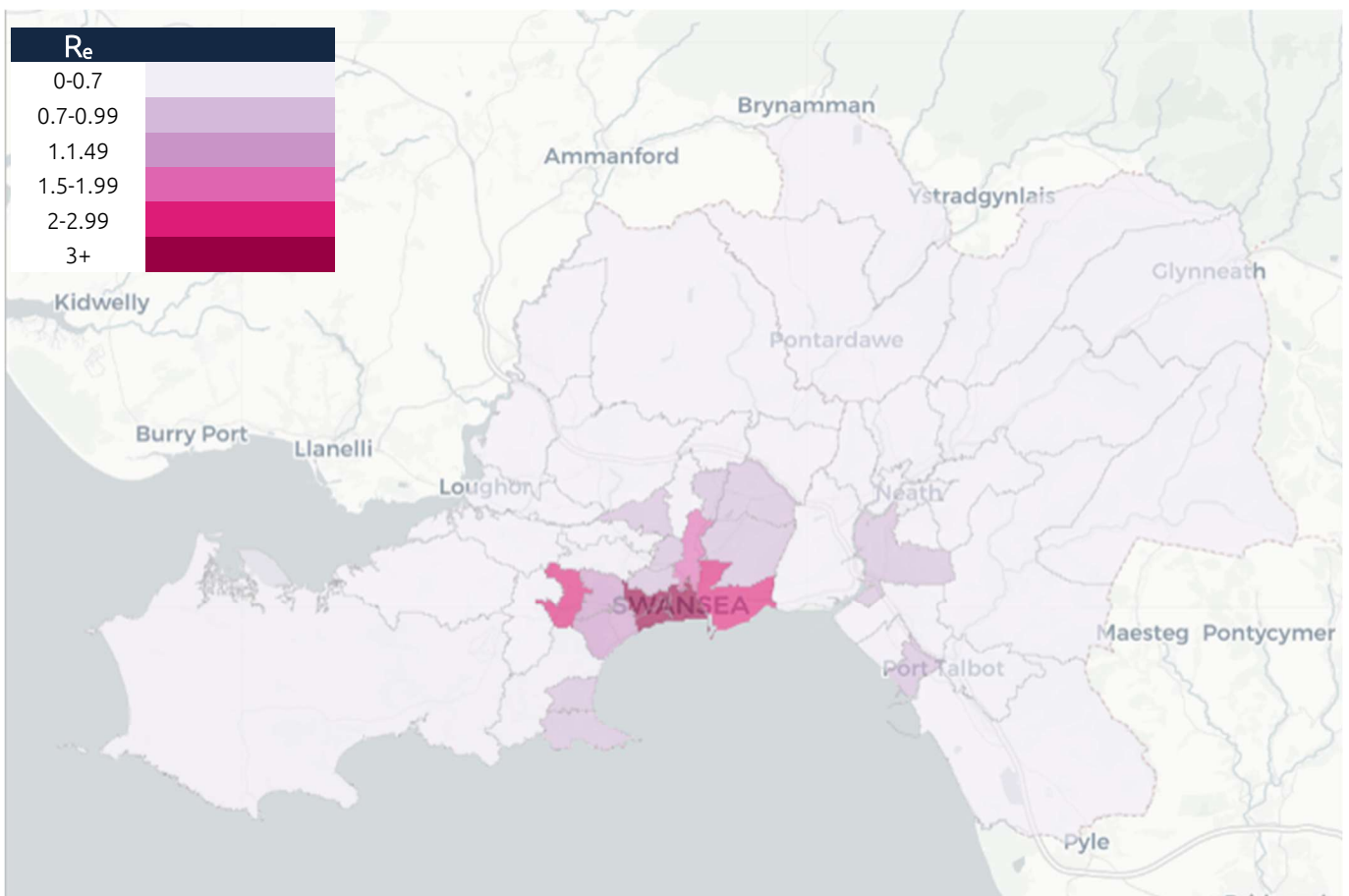


Figure 9 Map of all MSOA in the Swansea Bay University Health Board area showing the modelled value of Re (where $Re > 1$ a major outbreak could be sustained)

3.3. Baseline Output - Age Group Contribution

3.3.1. Children and young people

When examining the shape distribution of R_e values for each age category (Figure 10), it is evident that the mode of the R_e values is largest in the 0-4 age group indicating that this group most commonly has the highest level of risk. This is unsurprising as those age 0-1 are considered to be unprotected as infants are not vaccinated, and the majority of those aged between 1-4 have only had a single dose reducing their protection. However, despite this, the width of the distribution is narrow, showing substantially less variability. All MSOAs have age specific R_e values <1 for the 0-4 age group.

When the distributions are considered for the remaining age groups, it is clear that the most common value of R_e in an age group in an area being greater than 1 increases with age. This is partly a factor of increased age specific attack rates within the NGM, however, the shape of the curves also shows increased skew to the right, showing that there is increasing variability and an increasing number of MSOAs where the risk of outbreaks is high.

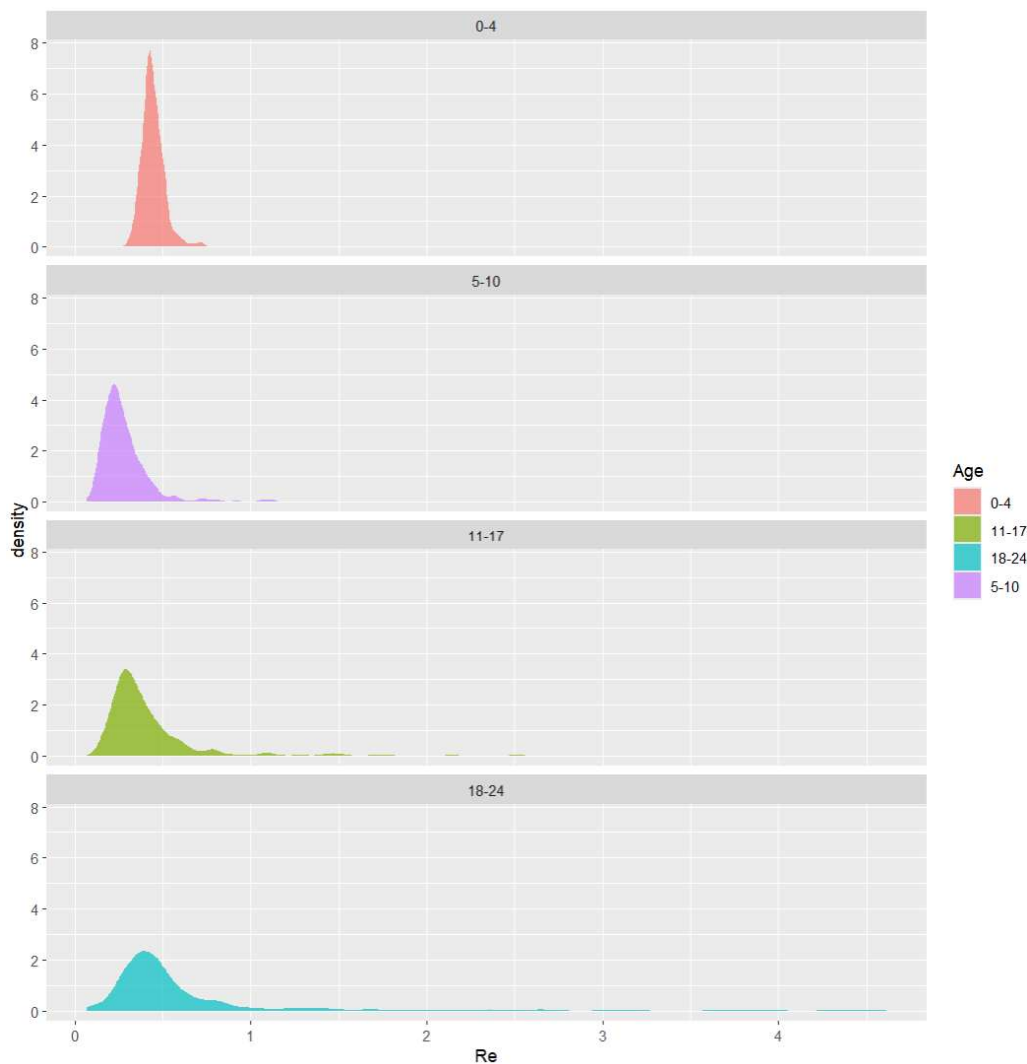


Figure 10 - Density of age-specific R_e values in all MSOAs in Wales

3.4. Sensitivity analysis

3.4.1. Vaccine effectiveness

When pooled results from a number of vaccine effectiveness studies were used to predict the potential risk of measles transmission (Figure 11), there was an increase in the risk, and the number of areas which could sustain an outbreak. Within the population there are relatively few individuals with only one dose of MMR, so the increased vaccine effectiveness from 90% to 95% has only a moderate impact. Conversely, the majority of individuals in the population have had two doses of MMR, so the reduction in vaccine effectiveness from 99% to 96% has resulted in a substantial increase in the number of susceptible individuals with 30 additional people susceptible to measles for every 1000 fully vaccinated individuals.

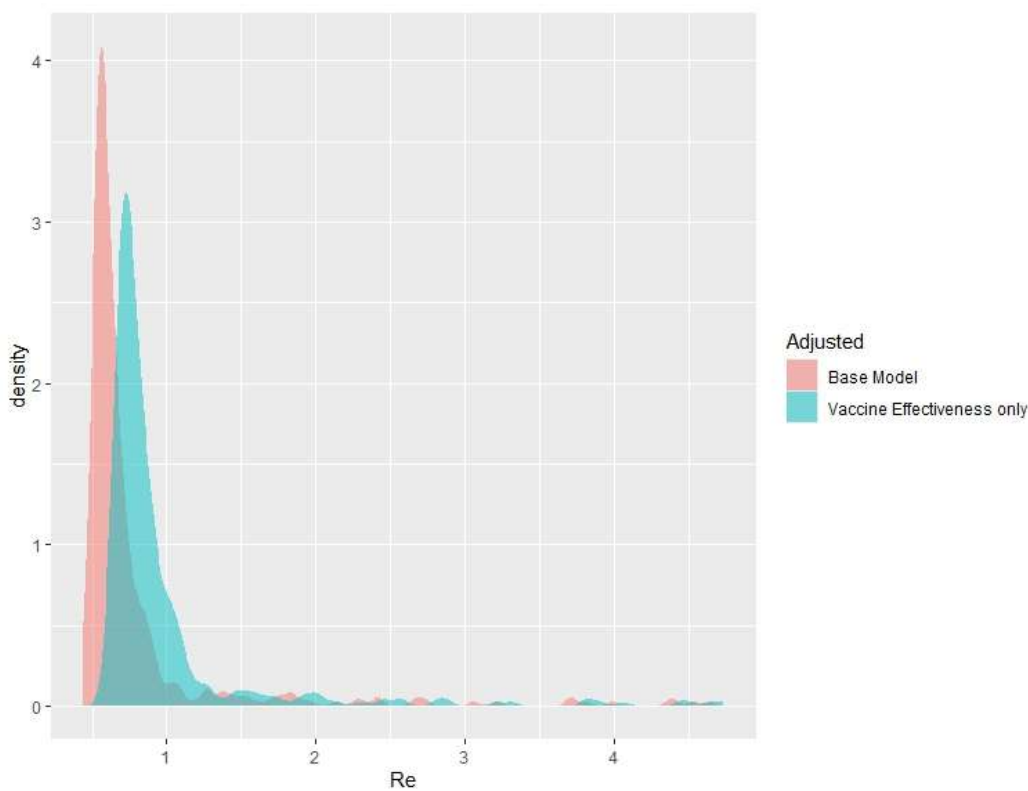


Figure 11 – Density distribution showing on R_e values for MSOAs in Wales with adjusted vaccine effectiveness values based on di Pietrantonio et al compared to those in the base model

Table 11 – Number of MSOAs in each health board area with $R_e > 1$ or where R_e is < 1 and either above or below the WHO threshold for effective elimination ($R_e = 0.7$) following sensitivity analysis for vaccine effectiveness (change from base model in brackets).

Health Board	Number of MSOAs				
	$R_e < 0.7$	$R_e = 0.7-1$	$R_e = 1-2$	$R_e = 2-3$	$R_e = 3-5$
Aneurin Bevan	20 (-35)	47 (+32)	9 (+2)	1 (+1)	0 (0)
Betsi Cadwaladr	27 (-50)	55 (+45)	10 (+4)	2 (+1)	0 (0)
Cardiff and Vale	9 (-21)	27 (+14)	17 (+6)	5 (+4)	5 (0)
Cwm Taff Morgannwg	23 (-31)	32 (+30)	1 (+1)	1 (0)	0 (0)
Hywel Dda	2 (-30)	35 (+20)	11(+10)	0 (0)	2 (0)
Powys	3 (-10)	12 (+7)	4 (+3)	0 (0)	0 (0)
Swansea Bay	6 (-24)	30 (+18)	8 (+5)	3 (+1)	3 (0)
Wales	90 (-201)	238 (+166)	60 (+31)	12 (+4)	10 (0)

In most instances the largest risk group in each MSOA remains the 18-24yr olds, however there are more MSOAs where the R_e value for 11-17 year olds exceeds one and the contribute substantially to the risk of sustained transmission. In this scenario, the majority of MSOAs in Wales are above the WHO threshold for elimination. It is important to note that the sensitivity analysis changes the magnitude of any risk, but does not change which areas have the highest risk, or which groups contribute most to that risk.

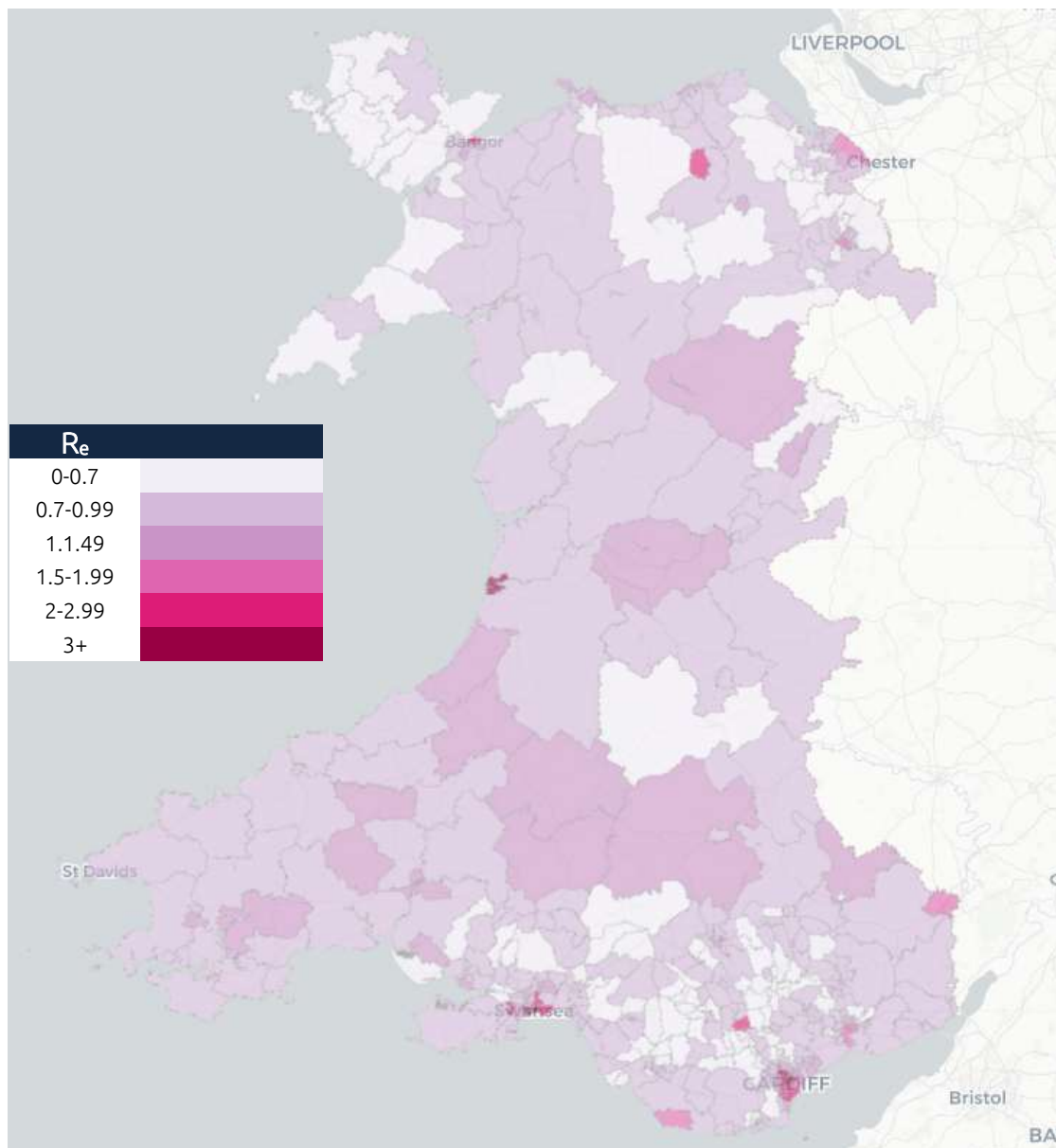


Figure 12 - Map of all MSOA in Wales showing the modelled value of R_e (where $R_e > 1$ a major outbreak could be sustained) after application the vaccine effectiveness estimates published by Pietrantonio et al

Where R_e remains greater than 1 following application of the correction factor there is a linear relationship between the predicted size of any outbreak. This suggests that there is an approximate 4% increase in the size of the theoretical outbreak.

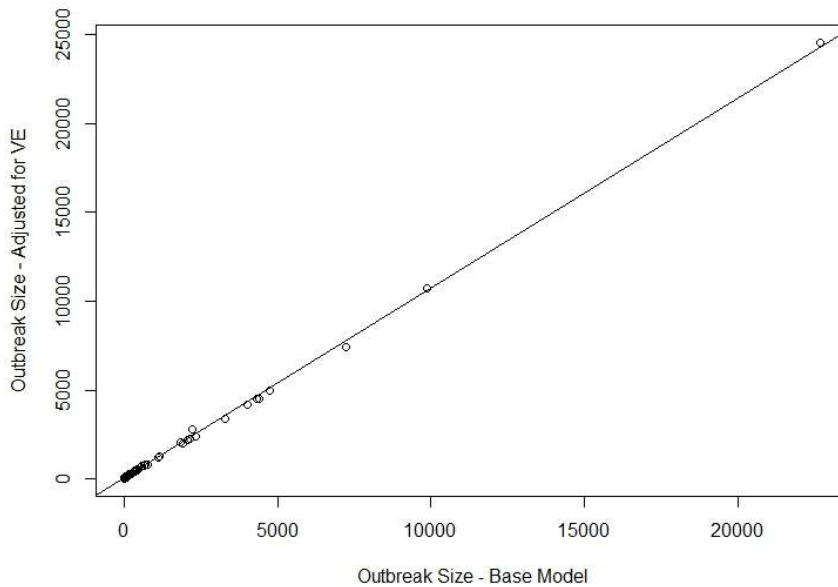


Figure 13 - Relationship between modelled maximum outbreak size with and without adjustment for vaccine effectiveness

3.4.2. Underestimation of vaccine coverage

When the factors were applied to examine the effect of underestimation of vaccine coverage within the model, the distribution of R_e values moves to the left, and number of MSOAs where R_e was greater than 1 reduced to 31 (Figure 14-14, Table 12). Using these assumptions, the majority of MSOA in Wales are below the WHO threshold for elimination. However, despite the very large correction factors for older age groups transmission in areas is still predominantly driven by 18-24 year olds. Within the NGM the R value for transmission within the 18-24 group (8.72) is higher than all other values, including that of intergroup transmission for 11-17 year olds (7.52). This means that to reduce R to the same amount, it requires higher coverage of the population. So even in an area where the coverage in 18-24 year olds is the same as for the 11-17 year old population, the older group will present highest risk of transmission.

Where R_e remains greater than 1 following application of the correction factor there is a linear relationship between the predicted size of any outbreak (Figure 16). This suggests that there is an approximate 40% reduction in the size of the predicted outbreak. This shows that potential outbreak size is susceptible to uncertainty in the vaccination status of the population. However, areas where a substantial outbreak is believed to be possible, will still support very significant outbreaks even with a large correction factor applied.

Table 12 – Number of MSOAs in each health board area with $R_e > 1$ and major outbreaks could take hold, or where $R_e < 1$ and either above or below the WHO threshold for effective elimination following adjustment for vaccine coverage (change from base model in brackets)..

Health Board	Number of MSOAs				
	$R_e < 0.7$	$R_e = 0.7-1$	$R_e = 1-2$	$R_e = 2-3$	$R_e = 3-5$
Aneurin Bevan	68 (+13)	3 (-12)	6 (-1)	0 (0)	0 (0)
Betsi Cadwaladr	84 (+7)	6 (-4)	4 (-2)	0 (-1)	0 (0)
Cardiff and Vale	41 (+11)	9 (-4)	8 (-3)	4 (0)	1 (-4)
Cwm Taff Morgannwg	55 (+1)	1 (-1)	1 (+1)	0 (-1)	0 (0)
Hywel Dda	42 (+10)	6 (-9)	0 (-1)	1 (+1)	1 (-1)
Powys	18 (+5)	1 (-4)	0 (-1)	0 (0)	0 (0)
Swansea Bay	40 (+10)	4 (-8)	3 (0)	1 (-1)	2 (-1)
Wales	348 (+57)	30 (-42)	22 (-7)	6 (-2)	4 (-6)

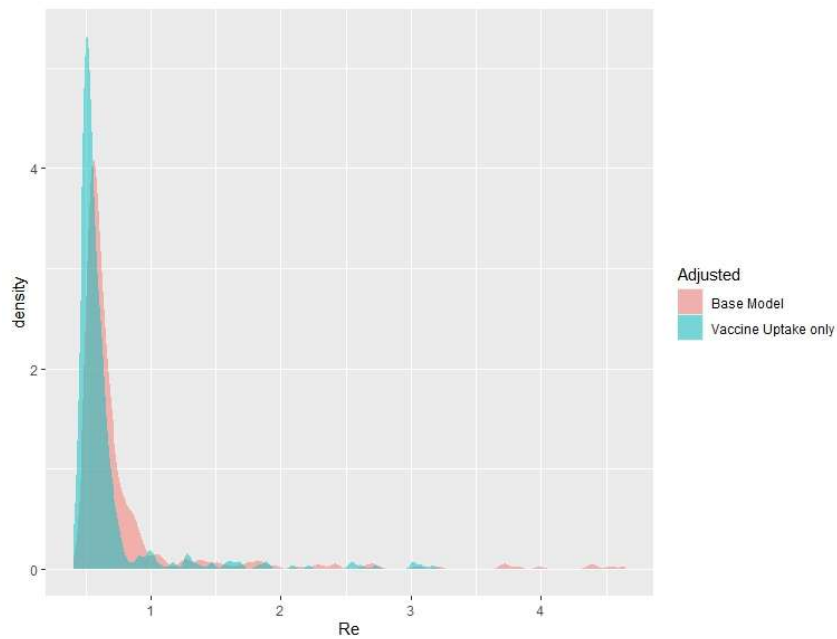


Figure 14 – Density distribution showing on R_e values for MSOAs in Wales with application of the adjustment factor for underreporting (Yes) compared to the base model assumptions (No)

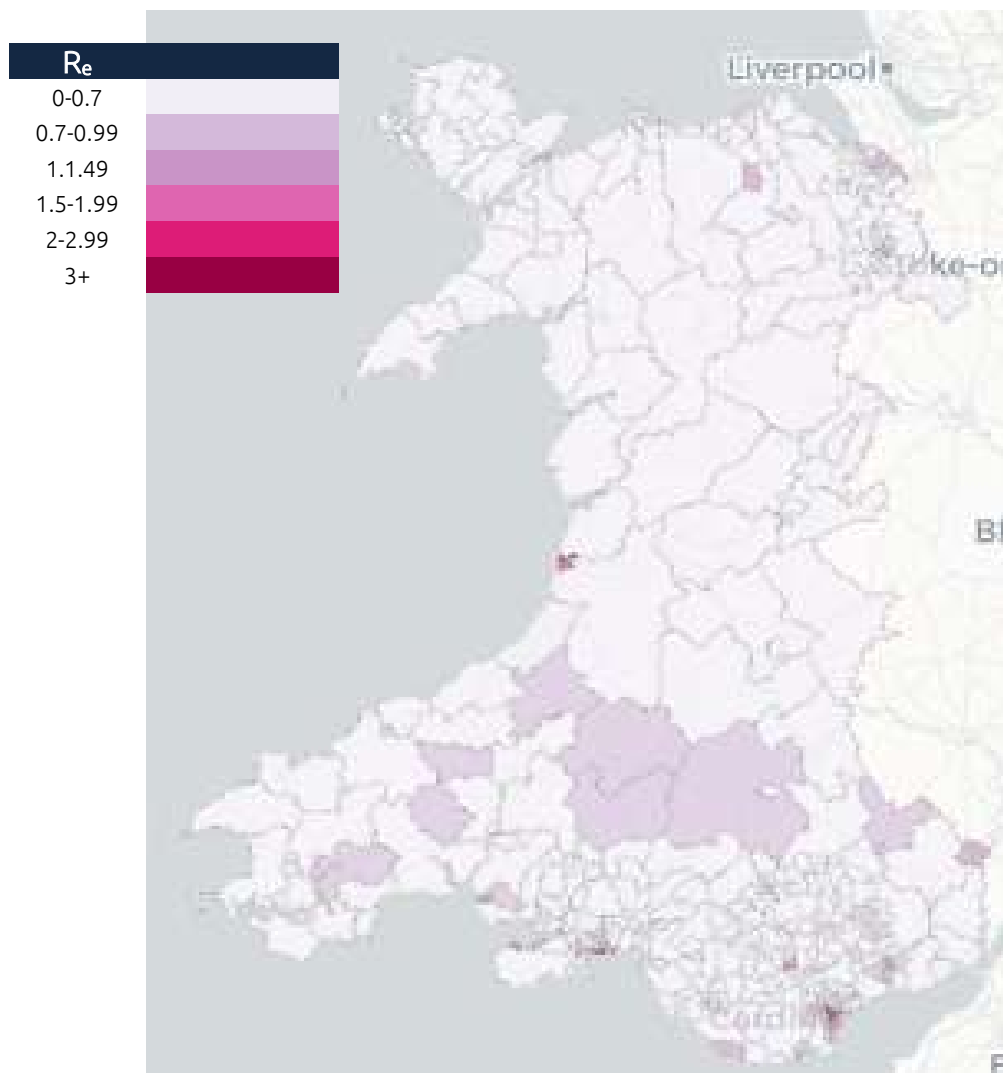


Figure 15 - Map of all MSOA in Wales showing the modelled value of R_e (where $R_e > 1$ a major outbreak could be sustained) after application of correction factor for under-reporting of vaccine uptake

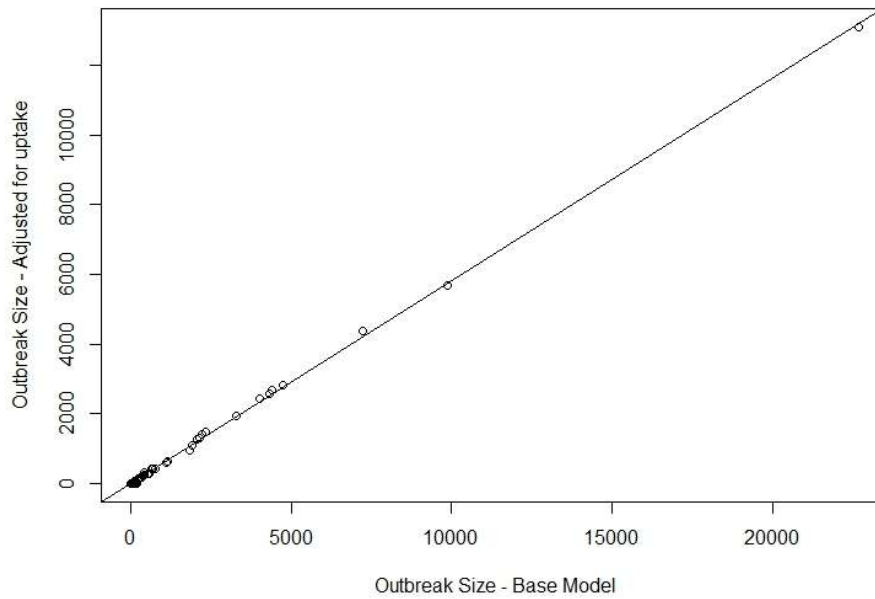


Figure 16 - Relationship between modelled maximum outbreak size with and without adjustment for under-recording applied

3.4.3. Adjustment for vaccine effectiveness and underestimation of uptake

The impact of these two variables on the modelled R_e value act in opposite directions, with uncertainty in vaccine effectiveness increasing the possible risk, and uncertainty in vaccine uptake reducing it. When these two factors are both applied the combined effect is an output which is slightly higher risk than predicted by the base model (Figure 17) for most areas, however, at the extremes where the risk of a large outbreak is highest the risk is reduced compared to the base model (Figure 19). This shows that the two factors are impacting on different areas, with uncertainty in vaccine effectiveness having most impact where uptake is highest, and underestimation of uptake having a larger effect where uptake is lowest. The result of this model is that there are more areas where R_e exceeds one than in the base model, however, the theoretical magnitude of any outbreak in the highest risk areas is lower (Table 13, Figure 18).

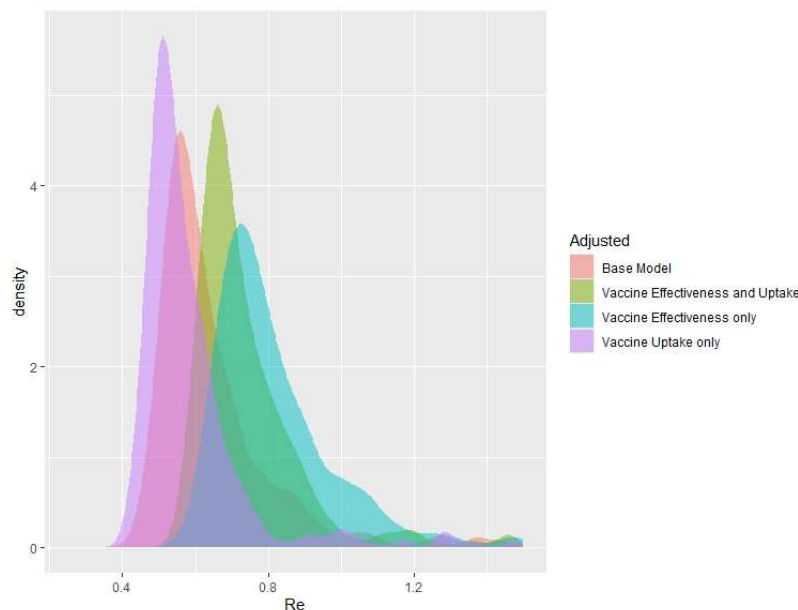


Figure 17: Density distribution showing on R_e values for MSOAs in Wales with application of the adjustment factor for underreporting of uptake (Vaccine Uptake Only), Vaccine Effectiveness (Vaccine Effectiveness only) and both (Vaccine Effectiveness and Uptake) compared to the base model assumptions.

Table 13 – Number of MSOAs in each health board area with $R_e > 1$ and major outbreaks could take hold, or where $R_e < 1$ and either above or below the WHO threshold for effective elimination following adjustment for vaccine coverage and effectiveness (change from base model in brackets).

Health Board	Number of MSOAs				
	$R_e < 0.7$	$R_e = 0.7-1$	$R_e = 1-2$	$R_e = 2-3$	$R_e = 3-5$
Aneurin Bevan	38 (-17)	32 (+17)	7 (0)	0 (0)	0 (0)
Betsi Cadwaladr	58 (-19)	30 (+20)	6 (0)	0 (-1)	0 (0)
Cardiff and Vale	20 (-11)	26 (+13)	10 (-1)	6 (+2)	1 (-4)
Cwm Taff Morgannwg	46 (-8)	10 (+8)	1 (+1)	0 (-1)	0 (0)
Hywel Dda	12 (-20)	36 (+21)	0 (-1)	1 (+1)	1 (-1)
Powys	6 (-7)	13 (+8)	0 (-1)	0 (0)	0 (0)
Swansea Bay	21 (-9)	21 (+9)	5 (+2)	1 (-1)	2 (-1)
Wales	201 (-90)	168 (+96)	29 (0)	8 (0)	4 (-6)

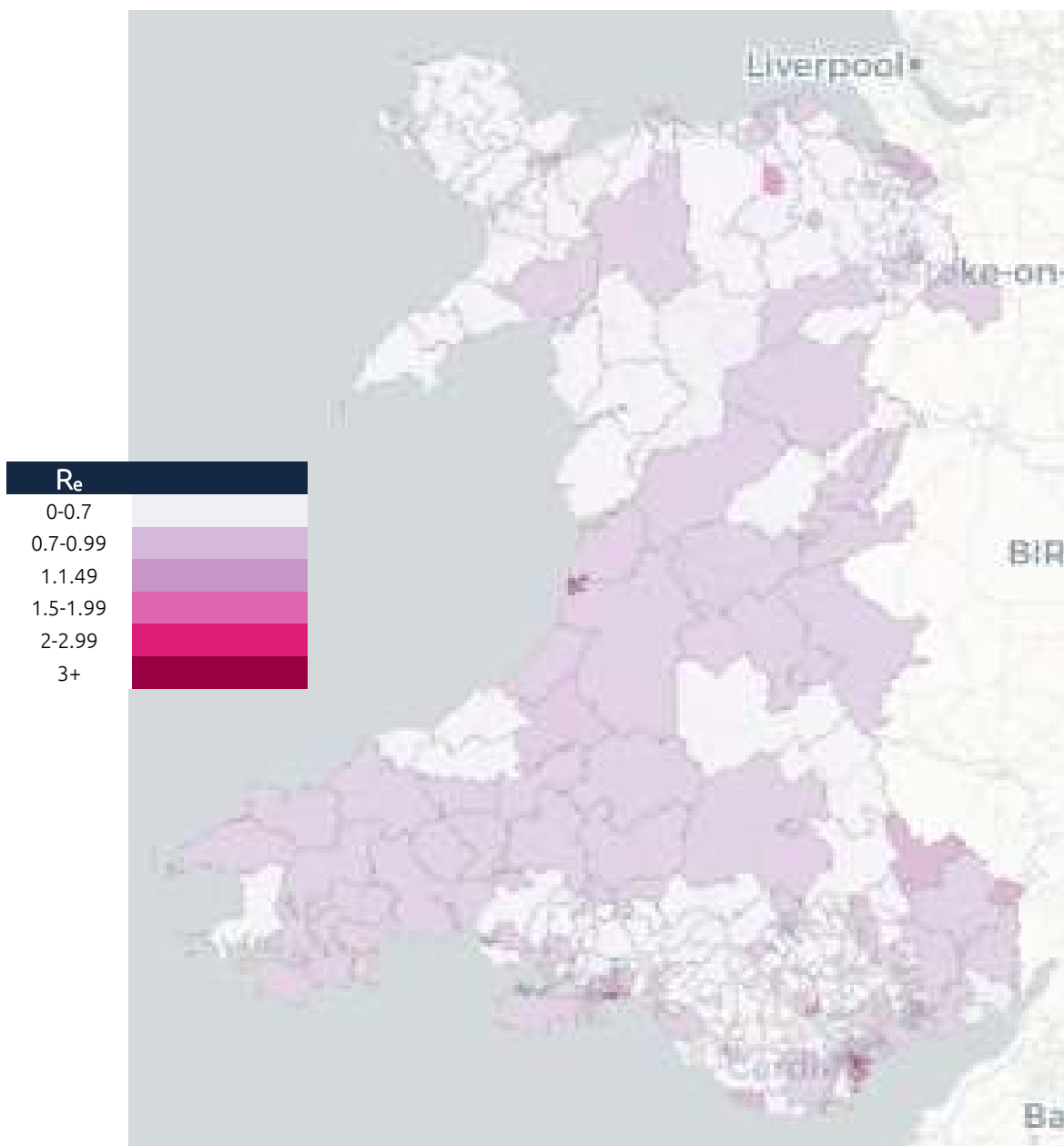


Figure 18 - Map of all MSOA in Wales showing the modelled value of R_e (where $R_e > 1$ a major outbreak could be sustained) after application of correction factor for under-reporting of vaccine uptake and vaccine effectiveness

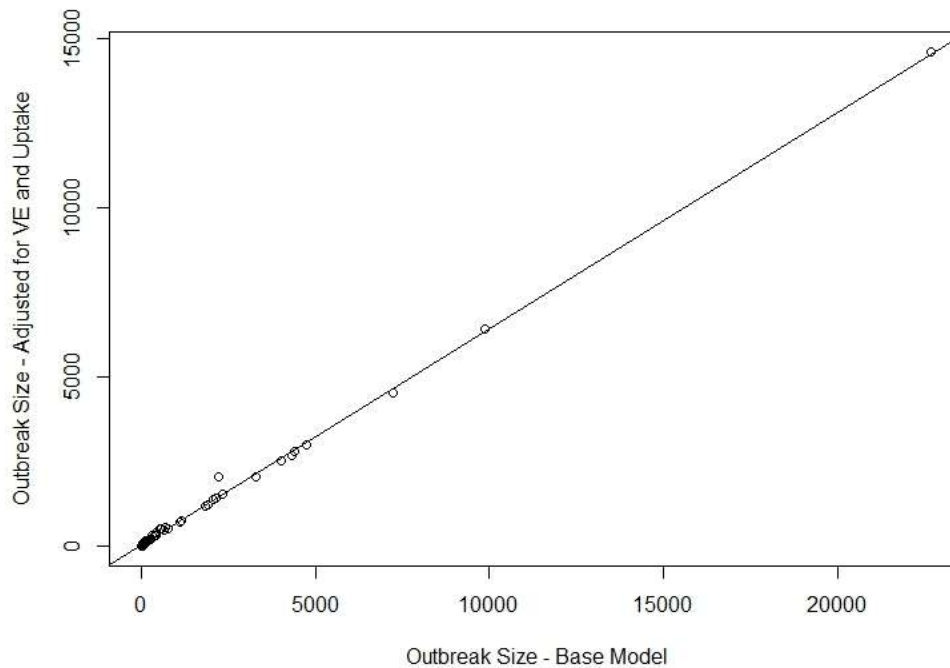


Figure 19 - Relationship between modelled maximum outbreak size with and without adjustment for under-recording and vaccine effectiveness applied

3.4.4. Potential Outbreak Size

In the literature there have been two different approaches to estimating the size of a major outbreak in an area with a highly vaccinated population. The method by UKHSA estimates the outbreak size at twice the number of cases required to reduce R_e to 1. An alternative method was proposed by Wallinga *et al* (Wallinga, et al., 2005), which bases the estimate on the proportion of susceptible individuals, and estimates that if the size of the susceptible population is $>4.3\%$, then it can sustain a major outbreak with 1.6 cases for every additional susceptible individual.

Using both methods to estimate outbreak size shows a significant correlation between the two estimates. The Wallinga method in general estimates that an area can sustain a slightly larger outbreak, than the UKHSA method, but generally both produce similar estimates for the data provided (Figure 20).

In both models the use of a multiplication factor, means as susceptibility increases, the number of cases predicted exceed that of the total number of susceptible individuals in the area being examined. However, it is also very unlikely that in the event of a large outbreak it would be confined to the MSOAs where $R > 1$. Therefore, we can expect in all areas where a large outbreak is in progress that we will see a significant number of cases in surrounding areas, even if vaccination in those areas is sufficient to prevent them developing into large clusters of their own. This was observed during the measles outbreak in Swansea in 2013

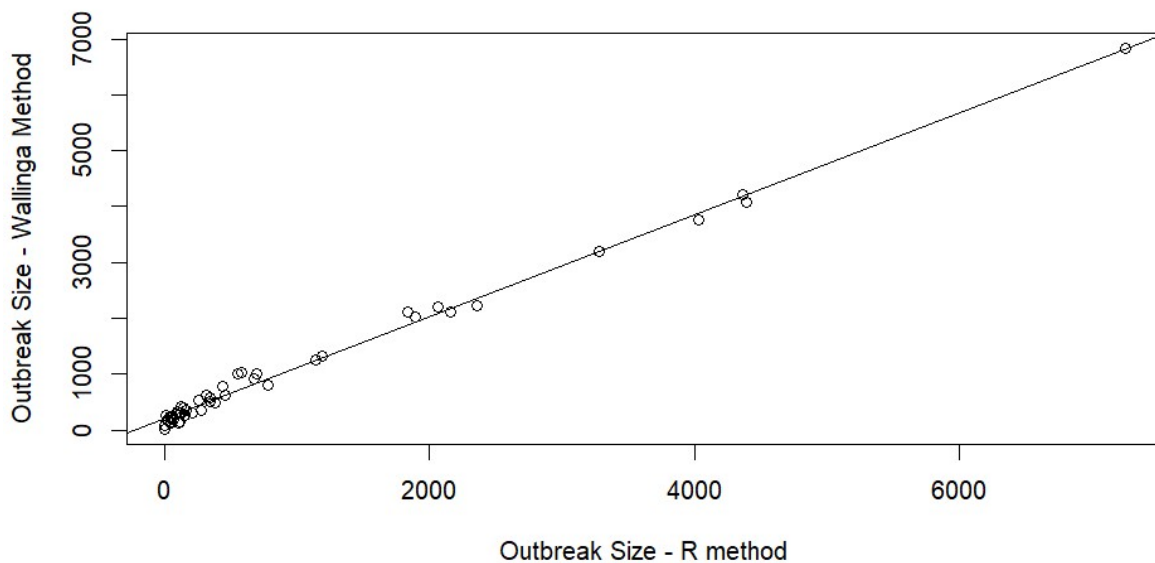


Figure 20 – Graph showing correlation between two methods of calculating potential major outbreak size

4. Discussion

The model indicates that there are very few areas in Wales where outbreaks of significant scale can be sustained. This does not preclude in any way smaller clusters of infection, spreading in these communities, where a single case can lead to transmission events in educational, healthcare or household settings. Nor does it mean that a case within a high-risk area will go on to cause a very significant outbreak.

However, the model does indicate that in some areas of Wales there is the potential, should wider community transmission be established, to cause very substantial outbreaks of infection. It is possible that within some areas, notably Cardiff, Newport and Swansea, the consequences of not preventing or being able to effectively respond to transmission could be an outbreak which could exceed that seen in 2012-13 in the Swansea area. An outbreak of this size would be very expensive to respond to. An analysis of the 2012 Liverpool outbreak with over 2458 reported cases over a four month period, put the cost of the response at £4.4m [£3.9m-£5.2m], over half of which was experienced by the NHS and Public Health bodies (Ghebrehewet, et al., 2016). This model suggests that several areas in Wales could sustain outbreaks of similar magnitude. However, it also has to be recognized that smaller outbreaks cost considerable amounts, in terms of the public health response, and the disruption to healthcare services from cases presenting there.

The model also suggests that the main driver of risk from measles in Wales is children and young people aged 11-25. There are clear data issues associated with the 18-24yr old age bracket, as at this age mobility increases, and records are not always updated and we know from published literature, that the inaccuracy of vaccination records increases with age. However, even when large correction factor are applied to compensate for this, 18-24 year olds still drive the transmission risks in Wales. It is important to note, that there are a number of communities where 11-17 age group drive or significantly contribute to the risk. Due to the high degree of mixing in these age groups, and the rapidity of transmission in school settings reducing risk these areas of risk should be a priority.



There are a number of other limitations in the model. Adults over 25 in Wales are considered to have a relatively consistent rate of susceptibility. This is likely to underestimate any risk of transmission in these groups. It is particularly problematic for modelling over time as more of the adult population derive their immunity from vaccination, and there is no accurate record. It is important to develop improved estimates of population susceptibility and any variation. If, as suggested in recent literature, there is more waning of protection from vaccine derived immunity, as the population becomes older, this older population will become more vulnerable, and better estimates are required to truly understand the drivers of risk. The estimates presented in this report also assume that reductions in susceptible numbers, following immunity developed in outbreak cases, is the only driver to stem the outbreak. In reality, this would not be the case and health protection actions to stem transmission often prevents escalation, however this may not always be possible.

A number of individuals born after 1970 would have also acquired natural immunity following measles infection, which was not accounted for in this model. There have been large outbreaks in Wales previously and some individuals who have moved into Wales from high incidence countries may have had measles infection. This is likely to impact estimates from high density urban areas disproportionately. Although, mixing patterns between different age groups has been accounted for, vaccination uptake is known to vary by other factors and mixing between different community groups with varying vaccination coverage is also likely to impact outbreak probability and maximum size.

Uncertainty in the parameters used in the model has some contradictory effects. Assumptions that impact on the effectiveness of vaccine have a higher impact on those areas where uptake is highest, and therefore lead to greater uncertainty around the general background risk in most areas. Conversely, uncertainty around uptake has the biggest impact on areas where uptake is lowest, and therefore leads to uncertainty around the size of any large outbreak should endemic community transmission be established. As these two factors impact different parts of the population, when they are looked at together they have an additive effect of increasing the predicted risk in highly vaccinated communities, whilst decreasing it in those with the areas with the highest predicted risk.

On average in recent years, Wales has seen a number of smaller outbreaks, following seeding from imported cases. This report does not predict that this pattern will change, but it does highlight that there is considerable risk of outbreaks in specific areas from transmission within some age groups. As things currently stand the model looks at the population risk at this current point in time. However, the development of a model for predicting risk will also allow for forecasting based on trends. It will be necessary to further develop the capability to see where problems and risk areas will arise in the future.

5. Recommendations

5.1. Prevention

Recommendation 1 - Ensure that a targeted risk based intervention to improving coverage in 11-17y olds and university aged teens/ young adults is included in the next WHC on measles elimination

Recommendation 2 – Vaccine Preventable Disease Programme to undertake work in partnership with local health boards to explore the underlying reasons for under-vaccination in school-aged children in Cardiff, Newport, Swansea and Denbigh



Recommendation 3 - Ensure that health board Immunisation teams and public health teams are aware of outbreak risk, particularly in the areas and age groups identified in this report

Recommendation 4 – Include measures to improve the active offer of MMR vaccination and recording of vaccination status at secondary school and university entry in the next WHC on measles elimination.

Recommendation 5 – Include measures to improve the recording of vaccination status on GP records on first registration for new entrants and those previously resident outside Wales, including an active offer of MMR to those without recorded history.

Recommendation 6 – Reinforce the need for vaccination checks on new registration with GPs and offer of vaccination inline with UK schedule where vaccine status is uncertain.

5.2. Response

Recommendation 7 – The health protection team should have high index of suspicion for cases in teenagers and young adults as they have the largest capacity for spread

Recommendation 8 – Consider further epidemiological factors including location, ethnic group or age in risk assessment and prioritisation methodology

5.3. Further work on model development

Recommendation 9 – Explore the potential for sero-study data to help understand susceptibility patterns in those 25y and older and improve the understanding of the role they play in the risk of larger outbreaks

Recommendation 10 - Build in waning of immunity into the model to understand how this will impact on transmission in older age groups.

Recommendation 11 - Undertake forward modelling to understand how trends will impact risk going forward

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