

# AN EVALUATION OF THE AUSTRALIAN NATIONAL SEROSURVEILLANCE PROGRAM

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## Abstract

The Australian National Serosurveillance Program (ANSP) was established in 1997 to provide national estimates of population immunity to vaccine preventable diseases and inform immunisation policy in Australia. The 1st round tested opportunistically collected sera from pathology laboratories across Australia, a 2nd round was carried out in 2002, and a 3rd round of testing is currently ongoing using sera from 2007–08. This is the 1st systematic evaluation of the ANSP since its inception. Existing information and outputs from the ANSP were reviewed and used in conjunction with data collected from a survey of the program operators to evaluate the overall utility of the ANSP and the following system attributes; acceptability, stability, simplicity, flexibility, data quality, sensitivity, representativeness and timeliness. So far the ANSP has generated 26 peer-reviewed publications and provided useful data that have influenced and provided an evidence base for immunisation policy in Australia; for example informing mathematical models, which identified the need for the young adult measles-mumps-rubella immunisation campaign. However, difficulties have been encountered with obtaining enough samples for testing in the 3rd round currently being undertaken. This is a concern that has the potential to undermine the representativeness and stability of the system, and other methods of sample collection must be investigated. Serological surveillance is an important component of any comprehensive system for monitoring population immunity to vaccine preventable diseases and evaluating the effectiveness of immunisation programs. However, an effective ongoing program requires strong support to ensure it remains sustainable in an era when laboratory based population health research for the public good is becoming increasingly challenging. *Commun Dis Intell* 2010;34(1):29–36.

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## Introduction

Serological surveillance (serosurveillance) provides estimates of antibody levels against vaccine preventable diseases (VPDs) in the population and is an important surveillance component in conjunction with notification, hospitalisation, mortality and immunisation coverage data. The primary advantage

of serosurveillance is that it provides an indicator of population immunity induced both by immunisation and natural infection. Therefore it is a useful tool for informing immunisation policy, can be used to monitor trends in population immunity before and after changes in immunisation programs, and provides a rich source of data for disease modelling.<sup>1</sup>

National serosurveillance programs are well established in many countries, with at least 3 distinct models of sample collection employed. England and Wales,<sup>2</sup> Belgium, Bulgaria, Hungary, Ireland, Israel, Lithuania, Malta, Romania and Slovenia request representative laboratories to submit residual samples collected for routine laboratory testing that would otherwise be discarded, which is referred to as residual or opportunistic sampling.<sup>3</sup> The 2nd model is specific population-based random serum collection such as that undertaken by the Netherlands<sup>4</sup> the Czech Republic, Latvia, Luxembourg, Slovakia, Spain and Sweden.<sup>3</sup> Thirdly, in the United States of America sera are collected along with a wide range of other information from participants in population-based, randomly selected National Health and Nutrition Examination Survey.<sup>5</sup> The advantages and disadvantages of each method of serum collection have been discussed extensively elsewhere.<sup>1,2,4</sup>

The Australian National Serosurveillance Program (ANSP) was established as a collaboration between the National Centre for Immunisation Research and Surveillance (NCIRS) and the Centre for Infectious Diseases and Microbiology (CIDM), the Institute of Clinical Pathology and Medical Research using the 1st model described above. In the 1st round, opportunistically collected sera from all 8 Australian jurisdictions were tested in 1997–99,<sup>1</sup> the 2nd round was carried out in 2002, and the 3rd round of testing is currently ongoing, using sera collected in 2007–08 (Table 1).

This paper reports the findings of a formal evaluation of the ANSP that was conducted in 2008 to describe the surveillance system, to assess its attributes and to determine the usefulness of the data it generates for informing immunisation policy in Australia.

## Methods

Data sources used for the evaluation included existing information available at NCIRS regarding both the previous and current rounds of the ANSP,

discussions with the ANSP study co-ordinator at NCIRS and a survey of those involved in coordinating and overseeing the ANSP, both past and present. Existing information included a survey of participating laboratories conducted in March 2004 after the 2nd serosurvey regarding enabling factors and barriers to their involvement. All the relevant information and results of the survey were available at NCIRS. It was therefore decided that this information was sufficient to inform this aspect of the evaluation and repeating the survey of laboratories was not required.

The operator survey was sent to 10 people previously or presently involved with the ANSP, of which 9 (90%) replied. The participating laboratory questionnaire was sent to 67 personnel associated with 52 laboratories in 2004. Twenty-one laboratories (40%) completed and returned the questionnaire. Of these, 18 had contributed to the 1st serosurvey, 16 had again participated in the 2nd round and the remaining three had been invited but had not contributed to either.

The assessment of the ANSP usefulness and system attributes were adapted from the guidelines for evaluating public health surveillance systems produced by the US Centers for Disease Control and Prevention (CDC), which includes 11 attributes.<sup>6</sup> However, for the purpose of this paper only the 4 most relevant will be reported.

The usefulness and attributes of the ANSP were defined as follows:

- usefulness: the extent to which the ANSP system and data contribute to the control of vaccine preventable diseases in Australia;
- acceptability: the willingness and ability of contributing laboratories to participate in the ANSP;
- simplicity: the structure of the ANSP and the way it operates;
- representativeness: how representative the sample selected for inclusion in the serosurvey is of the Australian population;
- timeliness: the ability of the ANSP to produce results and reports in a timeframe that allows them to be used by stakeholders.

## Results

### System description

A detailed description of the ANSP has been given by Gidding<sup>1</sup> so only a brief outline will be included here. Information flow is summarised in the Figure and the antigens included in each round are listed in Table 1.

Ethics approval is obtained for each round of sample collection and participating laboratories may also seek their own individual approvals. Public and private sector diagnostic laboratories across all 8 Australian jurisdictions send residual serum

**Table 1: Antigens included in each round of the Australian National Serosurveillance Program**

	Serosurvey 1 1996–99	Serosurvey 2 2002	Serosurvey 3 2007–08
Laboratories participated/invited	45/52	37/50	27/49
Number of specimens collected	13,084	7,699	Collection ongoing
<b>Antigens included</b>			
Measles	✓	✓	✓
Mumps	✓		✓
Rubella	✓	✓	✓
Varicella	✓	✓	✓
Hepatitis A	✓		✓
Hepatitis B	✓	✓	✓
Hepatitis C	✓		
Diphtheria	✓		
Tetanus	✓		✓
Polio	✓		✓
Pertussis	✓	✓	✓
Meningococcal C		✓	✓
Cytomegalovirus		✓	
<i>Helicobacter pylori</i>		✓	

samples to CIDM. Exclusion criteria include infants less than one year of age, and subjects who are known to be immunosuppressed, HIV positive or have received blood transfusions in the previous 3 months. Laboratories are also requested to submit only 1 specimen of serum per person. Samples are tested for antibodies using immunoassays specific for the antigens of interest. Population immunity for each antigen is inferred using accepted immune correlates of protection. The results of the serosurveillance and resultant mathematical modelling or policy implications are reported to the relevant committees and working parties responsible for disease control and immunisation policy, and then published in peer-reviewed journals.

## Usefulness

The CDC guidelines define a public health surveillance system as useful if it 'contributes to the prevention and control of adverse health-related events, including an improved understanding of the public health implications of such events'.<sup>6</sup> A total of 26 papers arising from the first 2 rounds of the ANSP have been published in peer reviewed journals, which have covered issues such as evaluation of immunisation campaigns, reporting of baseline levels of immunity, mathematical modelling of disease transmission dynamics and the impact of immunisation programs (Table 2).

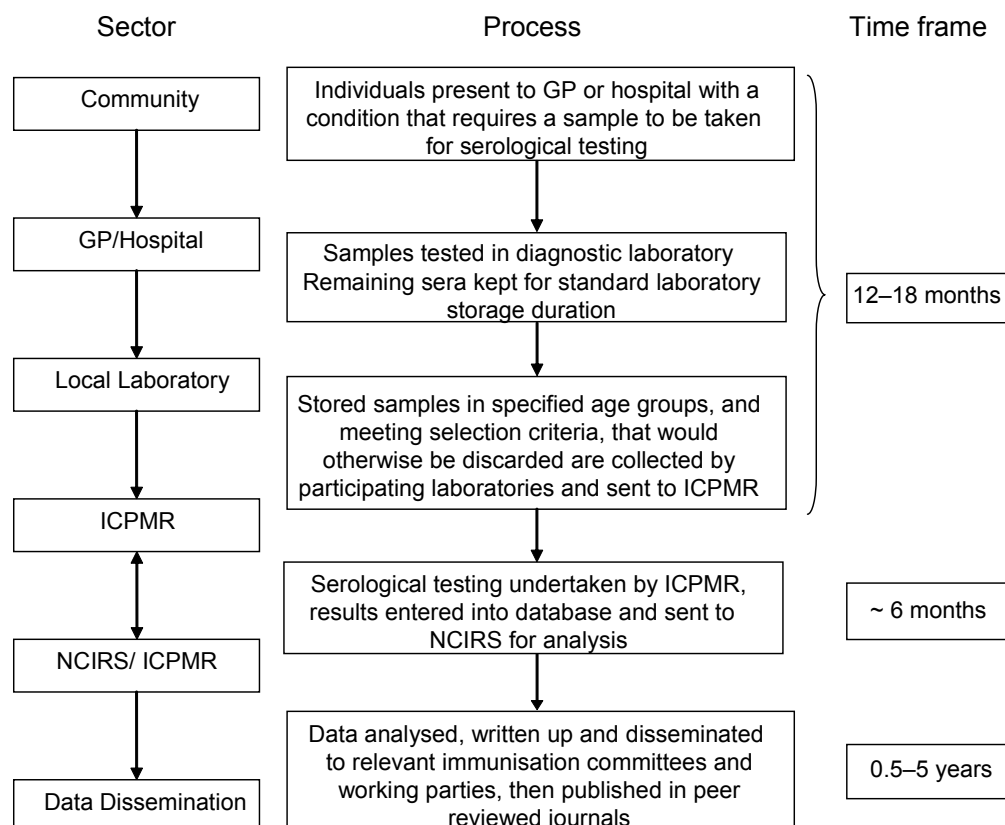
Overall, the ANSP meets the definition given above, particularly through its ability to contribute both conceptual knowledge, through increased understanding and stimulation of research into prevention and control of VPDs; and instrumental knowledge, through evaluation of immunisation programs and policy recommendations.

Specific objectives for the ANSP have not been defined, however the stated purpose is 'to measure the age-specific prevalence, in Australia, of susceptibility or immunity to diseases that are, or will soon be, vaccine preventable' by providing valid data for the 5 key outcomes listed below. The extent to which these outcomes have been achieved is examined.

### Outcome 1: To measure age group specific population immunity to vaccine preventable diseases in Australia

It is clear that the ANSP generates useful data for determining measures of age group specific population immunity to diseases that are, or could potentially become, vaccine preventable. This information is extremely valuable for informing immunisation policy when combined with data on vaccine coverage and disease notifications. Eleven of the research papers generated were produced specifically for this purpose as indicated in Table 2.

**Figure: Flow chart representing the Australian National Serosurveillance Program**



**Table 2: The Australian National Serosurveillance Program has generated 26 publications and provided a valuable evidence base for immunisation policy in Australia**

Study focus	Outcomes and/or policy recommendations
<b>ROUND 1</b>	
Discussion of serosurveillance	Outlines need for ongoing national serosurveillance in Australia <sup>1</sup>
Evaluation and/or discussion of vaccine program	Confirmation of measles control campaign (MCC) effectiveness and recommendation to continue serosurveillance in Australia using opportunistically collected sera <sup>7</sup>
Evaluation and/or discussion of vaccine program	Confirmation of MCC effectiveness <sup>8</sup>
Evaluation and/or discussion of vaccine program	Young adults should be encouraged to have a 2nd dose of measles-mumps-rubella (MMR) or serological confirmation of measles immunity <sup>9</sup>
Evaluation and/or discussion of vaccine program	Maintenance of high MMR coverage and collection of high quality surveillance data to detect and vaccinate non-immune females of child-bearing age <sup>10</sup>
Evaluation of laboratory testing procedures	Microimmune ELISA is a more appropriate assay than the Enzygnost ELISA for estimation of mumps seroprevalence <sup>11</sup>
Evaluation of sample collection methods	Opportunistically collected sera is a valid method serosurveillance as this method yielded similar seroprevalence estimates to a random cluster survey in Victoria <sup>12</sup>
Mathematical modelling	Sustained efforts are required to improve coverage with 2 doses of MMR and to ensure elimination of Indigenous measles transmission <sup>13</sup>
Mathematical modelling	Varicella vaccination should be aimed at children less than 5 years of age and further modelling using serosurvey data is warranted <sup>14</sup>
Population seroepidemiology	Ongoing need to improve MMR vaccine uptake in infants and recommendation of vaccination campaign targeting young adults <sup>15</sup>
Population seroepidemiology	Identification of young adult population group with low level of mumps immunity and recommendation to renew efforts to maximise MMR coverage <sup>16</sup>
Population seroepidemiology	Baseline population seroprevalence of varicella and mathematical modelling of disease transmission <sup>17</sup>
Population seroepidemiology	Any decision on national routine childhood hepatitis A vaccination requires a cost-benefit analysis before implementation <sup>18</sup>
Population seroepidemiology	People born in Asia are a high risk group for hepatitis B virus (HBV) infection in Australia and targeted vaccination of this group should be considered <sup>19</sup>
Population seroepidemiology	Higher evidence of past infection with HBV in the Northern Territory compared with Australian average for children aged ≤ 9 years <sup>20</sup>
Population seroepidemiology	Very low seroprevalence of immunity to hepatitis C virus in the over 50 years age group <sup>21</sup>
Population seroepidemiology	Additional efforts recommended to protect those aged over 50 years against diphtheria and tetanus, especially travellers <sup>22</sup>
Population seroepidemiology	Ongoing surveillance is required following the recent change back to inactivated polio vaccine <sup>23</sup>
Population seroepidemiology	Confirmation that changes in the scheduling of pertussis vaccination were necessary and recommendation for a sustained effort to ensure vaccination coverage remains above 90% for the benefit of herd immunity <sup>24</sup>
<b>ROUND 2</b>	
Evaluation and/or discussion of vaccine program	The young adult MMR campaign had no impact on measles immunity in Australia. To maintain elimination in the longer term, timeliness and coverage of childhood vaccination must improve and innovative strategies will be required to increase measles immunity among young adults <sup>25</sup>
Evaluation and/or discussion of vaccine program	The young adult MMR campaign had no impact on measles immunity in Victoria <sup>26</sup>
Evaluation and/or discussion of vaccine program	Varicella vaccination significantly increased immunity among children aged 3–5 years <sup>27</sup>
Evaluation and/or discussion of vaccine program	Demonstrated that the universal infant hepatitis B vaccination program was successful and that school-based programs for adolescents were effective <sup>28</sup>
Population seroepidemiology	Seroprevalence of antibody to meningococcus serogroup C was low before vaccine program introduction. Further serosurveys are required to evaluate vaccine impact <sup>29</sup>
Population seroepidemiology	High levels of cytomegalovirus exposure occur in the first few years of life therefore for a universal vaccination program to have maximal impact, the vaccine would need to be delivered to infants and have a long duration of protective efficacy <sup>30</sup>
Population seroepidemiology	Future <i>Helicobacter pylori</i> vaccines should be given in childhood as acquisition occurs from an early age <sup>31</sup>

### **Outcome 2: Identify groups in the population with low levels of protection to inform immunisation policy**

The key issue of identifying groups in the population with low levels of protection has been covered in a number of the ANSP publications. For example, immunity to diphtheria and tetanus was demonstrated to be less than 60% for adults aged 50 years or over in the 1st serosurvey, and the authors recommended a booster dose among this age group.<sup>22</sup> A cohort of young adults that remained susceptible to measles following the Measles Control Campaign (MCC) in 1998 was also revealed in the 1st serosurvey, which led to the further provision of Commonwealth funding for the young adult measles, mumps and rubella immunisation program in 2001.<sup>32</sup> Following this, subsequent further residual measles susceptibility was identified using ANSP data.<sup>12</sup> A birth cohort, between 1978 and 1982, with a relatively high level of susceptibility to mumps has also been identified from serosurveillance data, further underlining the importance of maximising 2 dose MMR coverage.<sup>16</sup>

### **Outcome 3: Provide baseline measures of immunity to determine subsequent trends in future serosurveys**

The 1st round of the serosurvey provided baseline estimates of immunity to 11 antigens, of which five were again included in the 2nd round along with 3 new antigens. The 3rd round included the 5 antigens from both previous serosurveys; four from the 1st round only and one from the 2nd round only (Table 1). Thus baseline estimates of age-specific susceptibility to 14 diseases that are or may soon be vaccine preventable have been published. Ten of these have been included in more than 1 round of the serosurvey, facilitating an examination of trends over time.

### **Outcome 4: Provide data for the evaluation of immunisation programs**

The primary reason for determining the baseline level of population immunity is to facilitate the evaluation of immunisation programs, and a number of papers dealt with this issue as shown in Table 2. For example the 1st round of the ANSP was designed specifically to evaluate the MCC using the MMR vaccine and demonstrated significant increases in population immunity to all 3 antigens.<sup>7</sup>

### **Outcome 5: Provide data for mathematical modelling of vaccine preventable disease dynamics**

Two papers developed mathematical models from ANSP data, to evaluate the impact of the MCC<sup>13</sup>

subsequent to the young adult MMR immunisation program,<sup>25</sup> to determine the potential for another measles epidemic to occur in Australia, and to postulate what must be done to prevent it occurring. Recent evidence has indicated that measles control initiatives have been successful and endemic measles has been eliminated in Australia.<sup>33</sup> Baseline data have also been used to model epidemiological parameters associated with disease transmission dynamics such as the level of herd immunity required to prevent ongoing transmission of varicella.<sup>14</sup>

In conclusion, the ANSP is a valuable part of the comprehensive surveillance system of VPDs in Australia and has provided a broad range of useful, policy relevant data. It appears that the ANSP has largely met its stated aims but, as discussed below, there are some issues that need to be resolved in order for the ANSP to remain a useful and effective serosurveillance mechanism.

## **Evaluation of selected system attributes**

### **Acceptability**

The decreasing ability of laboratories to participate in the ANSP is reflected by the number contributing samples in each round, which has declined from 45 in the 1st round, to 37 in the 2nd round and 27 in the 3rd round. Some, but not all, of this decrease can be attributed to the fact that there have been significant changes in the business environment for laboratories over the last decade, which has resulted in mergers and centralisation of diagnostic services. Eight laboratories that contributed to the 1st serosurvey are no longer in existence; on the other hand 5 laboratories contributed to the 3rd round that did not participate initially. Thus 15 laboratories that still exist dropped out in later rounds, indicating that barriers to participation exist.

The laboratory survey in March 2004 identified several such barriers, including the need to acquire additional ethics approval at the laboratory level and competing research and other operational priorities. A financial contribution by NCIRS to assist with labour costs for specimen collection was identified as necessary by 10 laboratories, while two were unsure. The remainder reported financial reimbursement was not required as staff time was the major barrier and any financial reimbursement went to the laboratory general revenue, rather than the individual staff member responsible for sample collection. Thus there was no motivation for staff to work outside their normal duties to assist with sample collection. Only nine of the 21 laboratories that responded (43%) reported that a trained technician, employed by NCIRS, could be of assistance with sample collection.



On the basis of these results, payment per specimen contributed was offered to laboratories contributing to the 3rd round of the ANSP. However only 3 laboratories actually invoiced NCIRS and this incentive does not appear to have been effective. Sample collection in the 3rd round has been slower than anticipated and as a result the sample collection period was extended.

### **Simplicity**

ANSP staff regard most components of the current system as relatively simple to operate. The centralised nature of the system greatly contributes to this as all samples can be tested quickly and easily without the need for complex inter-laboratory standardisation procedures. There is no specialised training required as all laboratory tests are part of routine practices at CIDM. The dataset is simple and small and seroprevalence estimates can be quickly generated upon the completion of laboratory testing. The majority (88%) of laboratories surveyed that participated in the 2nd serosurvey did not report any specific difficulties with sample collection. The two that did report difficulties indicated problems with using their laboratory database software to acquire the relevant information required for sample collection.

### **Representativeness**

For the ANSP to generate national seroprevalence estimates, the samples tested must be representative of the Australian population. Age, gender and jurisdictional representativeness are built into the sample size calculations. However, the increasing difficulty to collect sufficient samples has the potential to compromise external study validity. There are a range of other variables of which the serosurvey should ideally be nationally representative (e.g. ethnicity, rural/remote locality etc.), but due to ethical and data availability constraints this is not possible.

Representativeness cannot be directly inferred by the number of contributing laboratories participating, but the decreasing trend is a concern. If a large laboratory does not contribute samples this may impact on the geographical representativeness of the samples contributed to the ANSP.

Finally, the opportunistic sampling of serum samples submitted to laboratories for diagnostic testing utilised by the ANSP also has implications for the ability to generalise the data.<sup>1</sup> Individuals who have serum samples taken for diagnostic testing are not necessarily representative of the entire Australian population and it is difficult to identify and control potential biases that may arise from this approach, as detailed risk factor information is not available.<sup>2</sup> A study was undertaken to compare immunity levels in Victorian school children estimated using

ANSP opportunistic samples, by selecting results from Victorian subjects in the same age group, to a prospectively collected 3 stage random cluster sample. This demonstrated that similar estimates of immunity to measles, mumps, rubella, varicella and hepatitis B were generated by both sampling methodologies.<sup>12</sup> However the cost of sample collection and storage per antibody tested was over 7 times greater using the random cluster sampling compared with the ANSP opportunistic sampling. Random sampling is still the preferred methodology and would also overcome the difficulties encountered with obtaining samples from laboratories. However, this method also introduces potential biases, because it requires individual informed consent, the cost involved is prohibitive and it would require considerable dedicated funding to make it sustainable.

### **Timeliness**

Serosurveillance is an inherently slow process (Figure 1). Serology testing results do not affect the clinical management of patients, so timeliness is not absolutely imperative. However, samples should still be collected, processed and the results made available to the relevant committees and working parties as rapidly as possible to ensure that ANSP produces data which are relevant and up to date.

Increasing automation within the laboratory is improving the speed at which samples can be tested. However, as discussed previously, the primary rate limiting step is sample collection. There is also a need to ensure sufficient capacity is available to analyse and publish the results. ANSP data are primarily disseminated through peer-reviewed publication, which is also an inherently protracted process. As shown in Table 1 the majority of papers arising from both the previous serosurveys were published 3 to 6 years after the completion of sample collection. More immediate results are reported to the relevant advisory committees and working parties as part of the formal vaccine impact evaluations that NCIRS is contracted to provide but results are not widely available until publication in the peer-reviewed literature.

### **Discussion**

The first 2 rounds of the ANSP have generated useful data that have influenced and provided an evidence base for immunisation policy in Australia. However the key challenge for the ANSP lies in the increasing difficulties encountered with obtaining enough samples for testing. It is clear that the current method of sample collection is increasingly difficult to sustain, which has implications for all the system attributes discussed above.

Supplementary and alternative options for sample collection must be evaluated to ensure the ability to generalise the results to the Australian population and ongoing viability of the program. One option to increase engagement of laboratories and the acceptability of sample provision that has been considered is the establishment of jurisdictional-based serosurveillance systems. However this would greatly increase the complexity and cost of the system in order to standardise testing procedures and compromise the ability to generate nationally representative data.

It is important for the role and specific objectives of the ANSP to be clearly defined and communicated to all stakeholders. While peer reviewed publication is important, more immediate and regular feedback of results to participating laboratories may help to keep them engaged in the process and appreciate the importance of their contributions. Other approaches could include collaboration on resulting peer-reviewed publications, holding information dissemination forums, or the establishment of a formal consultation process, for example through the Public Health Laboratory Network, or creating a stakeholder reference group. Whilst all of these approaches are potentially useful, they are unlikely to address the fundamental problem of inadequate laboratory staff time available for sample collection.

Alternative options include collection of adult samples from blood bank donors, and request only paediatric samples from laboratories to reduce the collection workload. However as blood donors are restricted to healthy adults, such sample are not necessarily representative of the general population,<sup>34</sup> and would impact on the representativeness.<sup>35,36</sup> Furthermore individuals with certain diseases included in the ANSP (e.g. hepatitis B and C) are excluded from donating blood. The potential implications of this change in methodology would also need to be rigorously evaluated to ensure results would still be comparable with previous serosurveys, particularly for the in-house immunoassays.

Finally, there is also scope to strengthen the partnership between NCIRS, CIDM and the Commonwealth Department of Health and Aging by clearly defining the responsibilities of each organisation and establishing the ANSP as a cornerstone of VPD surveillance in Australia. An effective ongoing program requires strong support to ensure it remains sustainable in an era when laboratory-based population health research for the public good is becoming increasingly challenging.

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