Simplified lesson in capture-recapture methods and controversy regarding their epidemiological application

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Abstract

Capture-recapture methods, while not providing exact results, are an inexpensive approach to estimating the under-reporting of a given disease. Especially since 1980, capture-recapture has been commonly used in many surveillance and epidemiological studies. Most studies derive estimates of disease incidence rates based solely on the number of cases enumerated. These rates are typically biased low since 100% enumeration of cases is rarely achieved and more typically varies from 10% to 80%. The incidence rates in such studies are virtually uninterpretable and merely reflect the degree of reporting completeness. However, when two or more ascertainment sources are utilized to obtain reports of cases, the duplicate cases found in the ascertainment sources can be used to derive ascertainment-corrected incidence rates. It is then possible to compare results obtained in one study with that of other studies that have likewise derived ascertainment-corrected incidence rates, even though the percentage of reporting completeness may very in the different studies. When only two sources are used in capture-recapture methods, the estimate should be checked against a criterion ("gold") standard to validate the result. Public health officials were initially skeptical of application of capture-recapture methods to varicella disease due the seasonal distribution of cases; application of the method to herpes zoster cases also met with resistance due to the comparatively few cases reported.

Keywords: Capture-recapture, ascertainment-correction, varicella incidence

1. Introduction

Consider the following experiment: Suppose you have exactly 100 marbles in a jar, but I do not know this total number. I tell you that I can determine the number of marbles in the jar without counting them all. I ask you to let me draw 20 marbles from the jar. After I place a mark on them I have you put them back into the jar.

You mix the jar thoroughly, and I ask you to let me draw out 30 marbles this time. I find that 6 of these marbles are marked. At least statistically, this is what was expected since 20 out of 100 or 20% of the marbles in the jar were marked. We would expect that of 30 marbles drawn out of the jar this second time, $1/5^{th}$ (20%) or 6 marbles have marks.

Let ***B*** represent the number of marbles on the first draw (so ***B***=20). Let ***C*** represent the number of marbles on the second draw (so ***C***=30). Let ***A*** represent the number of marbles that were marked in the 2nd draw. Then ***BC***/***A*** is the estimate of the total number of marbles in the jar. Thus, we obtain (20)*(30)/(6)= 600/6 = 100 marbles.

If we did this experiment, say three times, we could average the number of marbles we computed in each experiment.

It is critical that the marked marbles are thoroughly mixed back into the jar following the first selection. If the marbles were not thoroughly mixed, this would result in bias and could make the capture-recapture result invalid. Especially if all the marbles in the first selection were placed together at the very bottom of the jar where it is unlikely I could reach them. The capture-recapture estimate in this case would be unusable and much too high. In fact, if no marked marbles were selected, it would not be possible to apply the formula with a zero denominator. Whereas, if all the drawn marbles were placed on the top of the jar, this would result in a capture-recapture estimate that would be biased too low.

The capture-recapture estimate (also called the Lincoln-Peterson or simply the Peterson estimate) is based on principles similar to those exemplified above.

2. Capture-Recapture Methods applied to Epidemiology

The assumptions inherent to the marble experiment given above are more formally given as follows:
1) The total number of marbles in the jar, N, (representing a population to be estimated) are unchanged from the 1st to 2nd trial selections. This is called a closed population--marbles are neither added nor removed.
2) All marbles are equally likely to be captured in each sample.
3) Marked marbles are not lost nor overlooked by the observer.

When applications are made to epidemiological studies, assumptions (1) and (3) above are often satisfied, however assumption (2) is often difficult to meet. There may be heterogeneity of capture probabilities. This means that individuals that seek health care for instance may behave differently. For example, parents may be more prone to take younger infants to a physician rather than older children. Also, parents may respond by taking a child with more serious disease to a physician; whereas no physician is sought for mild disease.

Capture-recapture refers to a statistical method that is used to adjust an estimate to reflect the level of reporting completeness. If a sample of ***a*** cases of a given disease appears on one list and a sample of ***b*** cases of that same disease appears on the second list, and ***c*** is the number of cases appearing in both lists, then an estimate of the population size, ***N***, is approximately given by ***N*** = (***a*** x ***b***)/***c***. These methods have been applied to calculations of abundance of wildlife, but increasingly they

doi: 10.1588/medver.2004.01.00004

have been used in epidemiological studies involving active surveillance systems [1-11].

The results of active surveillance in the Antelope Valley would have been uninterpretable or not comparable to other historical studies had capture-recapture methods not been utilized to estimate the true number of varicella cases and herpes zoster cases reported via active surveillance. When the reported varicella cases among 1- to- 19-year-olds in 1995 were ascertainment-adjusted, the varicella incidence rates by age closely compared to the "gold standard" of the 1990 to 1994 estimates from the National Health Interview Survey (NHIS) [12]. Capture-recapture indicated that varicella cases reported via active surveillance were only about 50% complete among individuals aged 1 to 19.

After varicella vaccine was introduced into the childhood immunization schedule in 1995, NHIS national incidence data were unavailable for comparison of subsequent years. The reporting completeness for combined years 1995 to 2001 based on verified varicella cases in individuals aged 5 to 19 years is 64% with an annual range of 60% to 69%. Interestingly, reporting completeness using capture-recapture methods in 1995, a year of high varicella incidence, closely compares to that of 1999 and 2000 where reported varicella cases of all ages were dramatically reduced by approximately 80% and 70%, respectively. Not surprisingly, when capture-recapture was applied to reported cases of herpes-zoster by the same sites that reported varicella (with the exception of one large HMO), again, there was a reporting completeness of 50% among individuals aged 5 to 19 during two years of active surveillance, 2000 and 2001.

The distribution of the value of the capture-recapture estimate is skewed in practice and so as to avoid misleading results associated with standard error, goodness of fit confidence intervals are computed for the capture-recapture estimate using an iterative algorithm that was developed based on the procedure outlined by R. R. Regal and E. B. Hook in *Goodness-of-fit based confidence intervals for estimates of the size of a closed population* [13]. A *Delphi IV* implementation of this algorithm is given in the computer program provided in Appendix I. The phrase "skewed in practice" indicates that the lower bound of the confidence interval (C.I.) was actually too low when based on standard error. When computed using goodness-of-fit, the lower bound is higher in value and better represents the likely lower bound.

An underlying assumption of capture-recapture is that the two ascertainment sources, schools and healthcare providers, are independent. However, often schools request that parents provide a physicians note to excuse the student's absence. Thus, it may be argued that the ascertainment sources are positively dependent causing the resulting estimate to be a likely lower boundary. This important detail was published by E. B. Hook and R. R. Regal in a letter, *Capture recapture methods*, published in *The Lancet* [14].

In the final analysis, while application of two-ascertainment source capture-recapture methods may not provide an entirely correct or exact number of the number of herpes-zoster cases, the key point is that it nevertheless provides a likely lower minimum of the number of herpes-zoster cases. The ascertainment-adjusted cumulative (2000-2001) HZ incidence rate is estimated to be 307 per 100,000 person-years among children aged <10 years with a previous history of wild-type varicella in the Antelope Valley. This likely minimum estimate is two-fold higher than that determined in the pre-licensure era via another study, the adolescent survey. Epidemiologists, however, do not like to do comparisons across different studies. Interestingly, the cumulative (2000 and 2001) ascertainment-adjusted HZ incidence rate of 138 per 100,000 person-years among individuals aged 10 to 19 years determined via active surveillance is the same as that reported by Hope-Simpson in the same age group in the pre-licensure era. This may indicate that CMI to VZV had not as yet declined substantially to cause increased HZ reactivation in this cohort. However, only recently during the past two to three years (beginning in 1999) did this cohort experience a dramatic decline in frequency of re-exposures to wild-type varicella. Thus, this cohort is more likely to have already had boosts to immunity because of prior re-exposure.

The close agreement of incidence rates among these various studies suggests that the limitations inherent to these studies, despite wide differences in study methodology, may have had no effect on the true incidence rates.

3. Controversy

Initially CDC public health authorities were reluctant to apply capture-recapture methods to varicella disease, and application to herpes-zoster was met with even greater resistance. On November 2, 2000, when a team from the CDC visited the Varicella Active Surveillance Project (VASP) office in Lancaster, CA (at High Desert Hospital), there was skepticism regarding use of capture-recapture methods. While it is true that there are relatively fewer cases of herpes-zoster compared to varicella cases reported via active surveillance, it must be kept in mind that herpes-zoster is a much rarer disease in children and adolescents when compared to varicella. Thus, wider confidence intervals are to be expected in herpes zoster studies conducted in a given study population. If, for instance, the VASP had collected a mere 10% of the cases, as might hypothetically occur using *passive* surveillance, the accuracy of capture-recapture results would be highly suspect. However, *active* surveillance captured approximately 50% of the HZ cases among children aged 5 to 19 years. While there were only 10 duplicate HZ cases reported in year 2000 (and 19 duplicates reported for combined years 2000-2001) by both ascertainment sources (schools and healthcare providers), this was a sufficient size according to D. S. Robson and H.A. Regier in *Sample Size in Petersen Mark-Recapture Experiments* [15]. This reference indicates when there are seven or more duplicate cases, there is 95% confidence that the theoretical bias is negligible, however, this does not account for any bias that might result from source dependencies or heterogeneity of the population within an ascertainment source [15].

One reference highlighting caution in using capture-recapture is Methods in Epidemiological Studies by C. Stephen [16]. Here the author does not state that the method should *not* be used, but "failure to address these issues [pertaining to satisfying the underlying assumptions of capture-recapture] can lead to inaccurate and sometimes misleading results."

Another reference, *Quantifying Unequal Catchability and it Effect on Survival Estimates in an Actual Population* states, "The biases … were less than 1% of the corresponding actual

doi: 10.1588/medver.2004.01.00004

value and were of an order similar to, or lower than, the sampling variation. They [the differences between the estimates and actual value] are therefore of little practical significance. The point is worth stressing since it has been claimed that capture-recapture methods are of little use in view of the failure of their underlying assumptions [17].”

In *Ascertainment-Corrected Rates: Applications of Capture-Recapture Methods* [18] the authors write, “When researchers employ active surveillance systems, they do not formally evaluate or correct for the degree of under-ascertainment. Undercount of cases is a potent determinant of rate which we cannot continue to ignore. We believe all rates should be adjusted for under-ascertainment in order to achieve a truer picture of the risk and risk factors of disease.” They continue, “Here we present a procedure to ascertainment correct rates based upon well established capture-recapture methods.” Another highlight in this reference states, “These methods are slowly making inroads into epidemiology, with the evaluation of the frequency and changing patters of ... We believe these techniques can be applied to complement existing disease monitoring systems, and have made capture-recapture methods the cornerstone for monitoring incidence in our WHO Multinational Project for Childhood Diabetes. …Because this method always evaluates and corrects incidence and prevalence estimates for the efficiency of registration (ascertainment), epidemiologists can be more confident that reported geographical differences in the frequency and rising rates of disease over time are not the result of as Sir Richard Doil stated ‘an increase in the efficiency of registration.’ Furthermore, the CI (confidence interval) constructed around these estimates indicate the level of enumeration and permit rational and meaningful comparisons of rates across populations.” The reference concludes, “We strongly urge that all rates be reported only after formal evaluation and adjustments for under-ascertainment have been completed [18].”

Interestingly, when my manuscript, “Using Capture-Recapture Methods to Assess Varicella Incidence in a Community Under Active Surveillance” was submitted for consideration by the Journal of the American Medical Association (JAMA), one of the peer-reviewers commented, “Justify why an accurate incidence rate is needed, versus some other method of capturing trends (but no incidence) such as sentinel reporting, passive case-reporting, etc.”

A public health official with the CDC at least initially believed application of capture-recapture methods to varicella disease to be invalid due to the seasonality of the disease. A peer-reviewer from *JAMA* finding no problem with seasonality wrote, “The authors need to explain why applying this technique to a common disease with seasonality is special.”

After taking into consideration the reviews provided by JAMA, the revised manuscript was next submitted to *The New England Journal of Medicine (NEJM)*. The Senior Deputy Editor for The New England Journal of Medicine wrote, “I am sorry to say that your manuscript, *Using Capture-Recapture Methods to Assess Varicella Incidence in a Community Under Active Surveillance*, is not acceptable for publication in the Journal. The manuscript was evaluated by in-house members of the editorial staff. We thought that it was interesting, but that its focus, content, and interest to our readers were such that it would not meet our needs. We therefore decided not to have it evaluated by any external reviewers, but to inform you promptly of our decision so that you can submit it elsewhere. Thank you very much for the opportunity to consider this manuscript. Sincerely yours.”

Finally, the manuscript was sent outside the U.S. to the European journal *Vaccine* where a peer-reviewer wrote, “The author studies the capture-recapture method for assessment of the varicella incidence in a closed community. This is an interesting methodological approach. The paper is well written and straightforward in methodology and presentation. Although its content is only marginally within the scope of *Vaccine*, generation of high-quality epidemiological data is the basis of every immunization program and thus of interest to vaccine-oriented scientists [19-23].”

Appendix 1. Example Delphi IV Computer Program: 2-Source Capture-Recapture Calculations

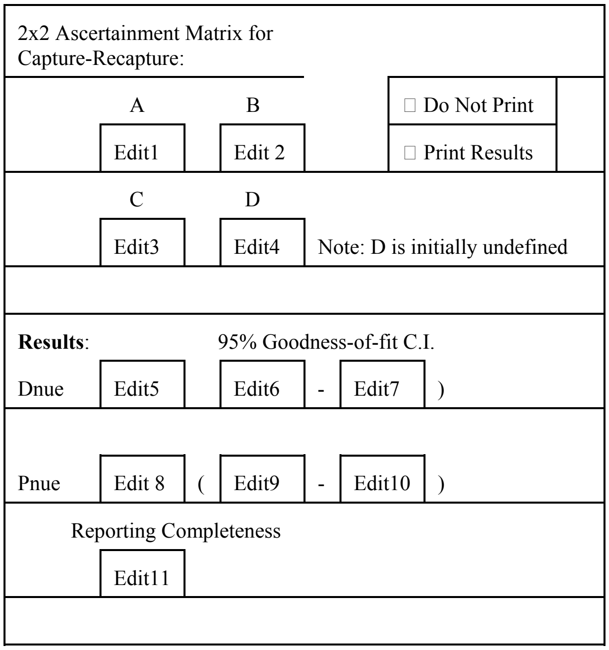
The Delphi IV “unit” below represents an example computer program that implements the capture-recapture calculations based on a researcher’s input of three variables ***a***–the number of cases reported by both ascertainment sources, ***b***–the number of cases reported by ascertainment source #1 only, and ***c***–the number of cases reported by ascertainment source #2 only. The procedure named “loopit” (shown in bold below) performs an iterative (looping) algorithm to derive the likely lower and upper boundary of the number of cases missed, represented by variable “**d**”, using a “goodness-of-fit” algorithm. The loop begins with the repeat statement and ends with the statement **until chisq>3.84.**

```
unit cr;

interface

uses Windows, Messages, SysUtils, Classes,
  Graphics, Controls, Forms, Dialogs,
  StdCtrls, ExtCtrls, Printers;
type
  TForm1 = class(TForm)
    Edit1: TEdit;Edit2: TEdit;Edit3: TEdit;
    Edit4: TEdit;Label1: Tlabel;
    Label2: TLabel;Label3: Tlabel;
    Label4: TLabel;Label5: Tlabel;
    Button1: TButton;GroupBox1: TGroupBox;
    RadioGroup1: TradioGroup;
  Edit5: TEdit;Label6: TLabel;Label7: TLabel;
  Edit6: Tedit;
    Label8: TLabel;Edit7: TEdit;Label9: Tlabel;
    Edit8: Tedit;
    Edit9: TEdit;Edit10: TEdit;Label10: TLabel;
    Edit11: TEdit;Label11: Tlabel;
    Label12: TLabel;Label13: TLabel;
    Label14: TLabel;Label15: TLabel;
    procedure FormCreate(Sender: TObject);
    procedure Button1Click(Sender: TObject);
  private
    { Private declarations }
  public
    { Public declarations }
  end;

var Form1: TForm1;
implementation
```

```
{$R *.DFM}

procedure TForm1.FormCreate(Sender: TObject);
begin
edit1.text:='';edit2.text:='';edit3.text:='';
edit4.text:='undefined';edit5.text:='';
edit6.text:='';edit7.text:='';edit8.text:='';
edit9.text:='';edit10.text:='';edit11.text:='';
end;

procedure TForm1.Button1Click(Sender: TObject);
  var na,nb,nab,n:smallint;lst:textfile;
      tabsp:string[5];ierr:integer;

procedure chartit;
  var a,b,c,d,apc,x,dnue,pnue,dlow,dhigh,
      plow,phigh,ppp:real;

      procedure gsquared(var a,b,c,d:real;
              var dlow,dhigh,nlow,nhigh:real);
        var dorig:extended;

        procedure loopit(cntr:integer);
          var v1,v2,h1,h2,t,v1th1,admbc,
              chisq:extended;
          begin
            v1:=a+c;
            h1:=a+b;
            v1th1:=v1*h1;
            repeat
              v2:=b+d;
              h2:=c+d;
              t:=h1+h2;
              admbc:=abs(a*d-b*c);
              if (v1th1>0.001) and
                ((v2>0.001) and (h2>0.001)) then
                chisq:=T*admbc*admbc/(v1th1*v2*h2)
              else
                begin chisq:=0.0; exit; end;
              d:=d+cntr;
            until chisq>3.84;
          end;

        begin
          dorig:=d;
          loopit(-1);
          dlow:=d+1.0;
          nlow:=a+b+c+dlow;
          d:=dorig;
          loopit(+1);
          dhigh:=d-1.0;
          nhigh:=a+b+c+dhigh;
        end;

  begin
    a:=nab*1.0;
    b:=(na-nab)*1.0;
    c:=(nb-nab)*1.0;
    apc:=nb*1.0;
    x:=n-na-c;
    d:=x;
    tabsp:='     ';
    if abs(a)>0.01 then dnue:=b*c/(a+1.0)
    else dnue:=0.0;
    edit4.text:=inttostr(round(dnue));
    writeln(lst,tabsp,datetimetostr(now));
    writeln(lst,tabsp,
     '                 SOURCE #2');
    writeln(lst,tabsp,
     'SOURCE 1  Reported      Missed        Total');
    writeln(lst,tabsp,
     '========  ============  ============        ============');
    writeln(lst,tabsp,'Reported  A=  ',a:8:0,'  B=              ',b:8:0,'  A+B=',na:8);
    writeln(lst,tabsp,'Missed    C=  ',c:8:0,'  D=              ',dnue:8:0,'
C+D=',c+dnue:8:0);
    writeln(lst,tabsp,'========  ============          ============
============');
    writeln(lst,tabsp,'Total     A+C=',apc:8:0,
      '  B+D=',b+dnue:8:0,'      ',na+c+dnue:8:0);
    pnue:=(a+b+1.0)*(a+c+1.0)/(a+1.0) - 1;
    writeln(lst,tabsp,'Dnue=B*C/(A+1)=',b:8:0,'*',
      c:8:0,'/(',a:8:0,'+1)=',dnue:6:0);
    writeln(lst,tabsp,'Pnue= (A+B+1)*(A+C+1)/(A+1) –
     1= (',a+b+1.0:4:0,')*(',a+c+1.0:4:0,')/(',
              a+1.0:4:0,') - 1 = ',pnue:4:0);
    if pnue>0 then ppp:=100*(A+B+C)/pnue
    else ppp:=0.0;
    writeln(lst,tabsp,'  Completeness:   ',
     '100*(A+B+C)/Pnue = 100*',a+b+c:4:0,'/',
     pnue:4:0,'=',ppp:7:2,'%');
    edit11.text:=format('%5.1f%',[ppp])+'%';
    edit5.text:=inttostr(round(dnue));
    edit8.text:=inttostr(round(pnue));
    dnue:=round(dnue);pnue:=round(pnue);
    gsquared(a,b,c,dnue,dlow,dhigh,plow,phigh);
    edit6.text:=inttostr(round(dlow));
    edit7.text:=inttostr(round(dhigh));
    edit9.text:=inttostr(round(plow));
    edit10.text:=inttostr(round(phigh));
    writeln(lst,tabsp,'  d-low=',dlow:8:0,
      '  d-high=',dhigh:8:0,
      '  p-low=',plow:8:0,
      '  p-high=',phigh:8:0,chr(12));
    writeln(lst,chr(12));
  end;

begin
  val(edit1.text,nab,ierr);
  if ierr<>0 then begin showmessage('Invalid integer in Cell A');exit; end;
  val(edit3.text,na,ierr);
  if ierr<>0 then begin showmessage('Invalid integer in Cell C');exit; end;
  val (edit2.text,nb,ierr);
  if ierr<>0 then begin showmessage('Invalid integer in Cell B');exit; end;
  na:=na+nab;
  nb:=nb+nab;
  if radiogroup1.itemindex=0 then
    assignfile(lst,'temp.dat') else assignprn(lst);
  rewrite(lst);
  if radiogroup1.itemindex=1 then
    begin
      printer.canvas.font.style:=[];
      printer.canvas.font.name:='Courier New';
      printer.canvas.font.size:=12;
    end;
  chartit;
  closefile(lst);
end;

end.
```

doi: 10.1588/medver.2004.01.00004

Windows Form:



Sample Output:

```
04/10/2003 8:53:36 AM

SOURCE 1  Reported     Missed       Total
======== ============ ============ ============
Reported  A=      222  B=     1296  A+B=    1518
Missed    C=      310  D=     1802  C+D=    2112
======== ============ ============ ============
Total     A+C=    532  B+D=   3098          3630
Dnue=B*C/(A+1)=1296*310/(222+1)=1802
Pnue=(A+B+1)*(A+C+1)/(A+1)-1=(1519)*(533)/(223)-1=3630
Completeness:100*(A+B+C)/Pnue = 100*1828/3630= 50.36%
 d-low= 1500 d-high= 2179 p-low= 3328 p-high= 4007
```

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doi: 10.1588/medver.2004.01.00004