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**Determinants of a bronchoalveolar lavage of good quality for mineralogical analyses in adults:  
Experience from the Asbestos Fibers and Particles Laboratory of Paris City**

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## Abstract

**Background:** Mineralogical analyses of bronchoalveolar lavage (BAL) may help in assessing past exposure to mineral particles. However, their interpretation relies on their quality, meaning their representativeness of the alveolar compartment. The aim of this study was to find predictive factors of BAL samples quality allowing a reliable mineralogical analysis.

**Methods:** All BAL samples analyzed between 2018 and 2020 in the Asbestos Fibers and Particles Laboratory from Paris City were included. They were read by an experienced cyto-pathologist and validated according to their representativeness of the alveolar region compartment. Univariate and stratified analyses were conducted to identify factors associated with the samples' cytological quality.

**Results:** On the 780 samples included, 64.4% were deemed of good cytological quality and 17.9% were not interpretable. Injected volume and BAL yield (recovery volume on injected volume ratio) were associated with cytological quality. Injecting at least 100mL with a  $\geq 60\%$  yield or injecting at least 150mL with a  $\geq 30\%$  yield allowed having a good proportion of BAL with sufficient cytological quality.

**Conclusions:** Injected volume greater than 100mL with sufficient BAL yield are essential factors to ensure a reliable mineralogical analysis of BAL samples.

**Keywords:** bronchoalveolar lavage; cytology; asbestos; silicosis; occupational diseases

## 1        **1. Introduction**

2        Exposure to mineral particles is known to be associated with diverse pulmonary, auto-immune diseases  
3        or cancer. For example, exposure to silica may cause pulmonary fibrosis (silicosis), lung cancer or  
4        scleroderma and asbestos may cause pulmonary fibrosis or cancer. However, it's often difficult to  
5        establish a causal effect between a past exposure to mineral particles and a determined disease. While it  
6        does not modify the therapeutic approach, finding the cause of the disease is important since it may  
7        allow compensation in case of occupational exposure [1]. The recognition process differs depending on  
8        the country, but it requires to confirm exposure to activities exposing to mineral dust. This may be  
9        challenging when no metrology was done or if the exposure is old. Searching for mineral particle in the  
10       bronchoalveolar lavage (BAL) may help provide evidence of past exposure [2–6]. Optic microscopy  
11       may be used to identify asbestos bodies (AB), which are marker of exposure to asbestos while electron  
12       microscopy is used to search for fibrous or non-fibrous mineral particles (silica, metals...). Several  
13       studies found a correlation between occupational exposure to asbestos and the number of asbestos  
14       bodies detected in BAL [7,8]. Furthermore, sample analysis of BAL proved to be an adequate tool to  
15       estimate pulmonary load in AB since there is a good correlation between the number of AB in BAL and  
16       the number of AB in the lung [9,10]. However, interpreting BAL mineralogical analyses can be  
17       difficult because they depend on the quality of the sample collected during the BAL. Guidelines agree  
18       on the fact that the volume of fluid injected must be at least 100mL (and less than 300mL) in order to  
19       have a reliable cytological analysis. This analysis also depends on a sufficient BAL yield and the  
20       absence of significant bronchial contamination [11–13]. However, the evaluation of practices is not  
21       carried out systematically, and to the best of our knowledge, there is no published study specifically  
22       concerning quality of BAL for mineralogical analysis.

23       The Asbestos, Fibers and Particles Laboratory (LAFP) located in Paris receives BAL from all over  
24       France for mineralogical analysis. The disparity of BAL collection practices has led to a systematic

1 cytological control of all samples sent to the laboratory. This cytological control is based on the  
2 counting of alveolar macrophages (AM) of a BAL sample on a Kova cell counting chamber to assess  
3 the sample's representativeness of the alveolar area. Indeed, AM represent the main resident cell  
4 population in the pulmonary alveoli and constantly found in BAL fluids. Data from published  
5 studies[14–19] allow setting a minimal number of AM for subject without pulmonary pathology of 40  
6 to 50 000 AM/mL of BAL and 180 to 200 000 AM/mL depending of tobacco intake (respectively for  
7 non- or former smokers and smokers) [11]. These numbers of AM may vary according to pulmonary  
8 diseases and quality of BAL [20]. Most chronic pulmonary diseases may increase the number of AM  
9 due to a local inflammatory reaction (alveolitis), and in contrast, the loss of alveoli caused by  
10 emphysema or fibrosis may be associated with a decrease of the number of AM. In addition, it has been  
11 reported that the total number of cells collected increases with increasing injected volume, and to a  
12 lesser degree with increasing yield [11]. A cytological qualification of all BAL yield received for a  
13 mineralogical analysis was set up at the LAFP. It was based on AM cell count and the smoking status.  
14  
15 The objective of this study was to specify the determining factors for obtaining a bronchoalveolar  
16 lavage sample of sufficient quality to be representative of the alveolar sector in case of a mineralogical  
17 analysis.

18

## 19 **2. Methods**

### 20 *2.1 Samples and patients' information*

21 All BAL sample received at the LAFP were systematically analyzed by a single experienced  
22 cytopathologist to assess their quality to ensure they were representative of the alveolar area. This  
23 analysis took into account the quantity and the type of cells observed in the BAL. All sample analyzed  
24 between December 2018 and October 2020 were included.

1 A form was completed by the health professionals who performed the BAL. From this document, the  
2 following variables were collected: sex, smoking status (non-smoker, or former smoker (smoking  
3 ceased for more than two years) and smoker) as well as number of pack-year smoked, the volume of  
4 saline solution injected (mL), the volume recovered (mL), the BAL yield (recovery volume on injected  
5 volume ratio) and the patient's reported disease.

6 After a descriptive analysis, the volume of the injected saline solution was divided in three categories  
7 (<100mL, 100-150mL, ≥150mL), as well as the BAL yield (<30%, 30-60%, ≥60%).

8 A cytological analysis by optic microscopy was performed on a 10µl of homogenized BAL sample  
9 which was dropped into a Kova cell chamber grid. Factors considered for this analysis were: the total  
10 number of cells, the number of AM, the number of bronchial cells and their ratio with macrophages.  
11 When the ratio of the number of bronchial cells divided by the number of AM was  $\geq 30\%$ , the BAL  
12 was considered bronchial. The sample was considered non representative if the concentration of AM  
13 was less than a minimal threshold (25 000/mL for non-smokers or ex-smokers and 60 000/mL for  
14 smokers).

15 The main outcome was the quality of the BAL sample assessed by the LAFP cytopathologist. A sample  
16 was considered of good quality if it was representative of the alveolar area of the lung. The  
17 qualification of each BAL sample examined is based on Table 1, with the establishment of a score  
18 taking into account the number of AM, the smoking status, and the level of bronchial contamination.  
19 This score, assessed only on the Kova cell observation, was elaborated according to data from the  
20 literature and the cytopathologist's experience of over 20 years of BAL analyses from patients with  
21 various pulmonary diseases. Three conclusions were possible from this analysis for a given sample:  
22 non-representative sample (NR), uncertain representativeness (UR) or representative sample (RS).

23 *2.2 Statistical analysis*

1 A descriptive analysis as well as univariate analyses were conducted to assess factors associated with  
2 the sample's good quality using ANOVA tests for quantitative variables,  $\chi^2$  tests or Fischer's exact test  
3 for qualitative variables, as appropriate. Analysis stratified on the volume injected were also conducted.  
4 All analyses were made using R software (version 4.0.4, packages "tidyverse", "compareGroups").  
5

### 6 **3. Results**

7 From December 2018 to October 2020, 780 samples were reviewed. Mean age of the population was of  
8 67.3 years. Approximately 64.4% (n = 502) of the samples were deemed of good quality for  
9 mineralogical analysis, 17.7% (n = 138) had uncertain representativeness and 17.9% (n = 140) were  
10 non-representative. Nearly 19% (n = 145) of the samples analyzed had missing data for the injected  
11 volume or recovered volume preventing the calculation of BAL yield. Missing data for BAL yield were  
12 more frequent in the UR group (26.1%) than in the NR (16.4%) or RS group (17.1%). Table 2 shows  
13 the results for the univariate analyses. Number of pack-years, injected volume, recovered volume and  
14 BAL's yield, were significantly associated with sample quality. As expected, each variable considered  
15 in the score for BAL's qualification (smoking status, number of AM and bronchial contamination) were  
16 significantly associated with sample quality (respectively p = 0.003, p <0.001 and p <0.001). Figure 1  
17 shows the distribution of the samples qualification by injected volume (A) and by yield (B).

18 Analyses stratified on injected volume are presented in Table 3. In the <100mL strata, for the 30-60%  
19 yield subgroup, slightly less than 50% of samples were of good quality and this percentage did not  
20 increase in the  $\geq 60\%$  yield subgroup. In the 100-150mL and  $\geq 150\text{mL}$  injected volume subgroups, the  
21 higher the yield, the higher the proportion of good quality samples they were. In the  $\geq 150\text{mL}$  injected  
22 volume subgroup, a yield between 30 to 60% or  $\geq 60\%$  allowed having a proportion of RS samples  
23 greater than 70% (respectively 73.4% and 90.8%). In the 100-150mL injected volume subgroup, only  
24 yields  $\geq 60\%$  had a proportion of RS samples greater than 70% (88.2%) (Table 3 and Figure 2).

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#### 4. Discussion

This study highlights the importance of having a good yield and a sufficient injected volume to obtain reliable mineralogical analysis results in BAL analysis. Reporting these two variables when requesting specific analysis on BAL such as mineralogical analyses is important. LBA procedures recommend discarding the first recovered fluid as it is considered a sampling of bronchial airways and non-representative of alveolar compartment [11]. Such procedure requires a minimal injected volume of 60 to 100mL saline solution. Indeed, if at least 100mL of saline solution was injected, a yield  $\geq 60\%$  allowed having almost always samples of good quality (nearly 90% of samples). However, some BAL may be difficult to carry out which may prevent reaching such percentage of yield. In the  $\geq 150\text{mL}$  strata, a yield between 30 and 60% allowed having suitable results in terms of cytological quality of sampling (proportion of BAL of good quality  $\geq 70\%$ ). Thus, when performing BAL for mineralogical analysis, if the yield is  $< 60\%$  with an injected volume of  $< 150\text{mL}$ , it seems appropriate to increase the injected volume, as long as the BAL is well tolerated by the patient, and it is not a BAL failure (less than 5% of the injected volume is collected) [11]. These results are consistent with data from the literature showing an increase in the number of cells collected as the injected volume increases [11]. Searching for AB and non-fibrous mineral particles in BAL can help better quantify past occupational or environmental exposure to mineral particles. They support suspicions of exposure when direct measurements of exposure in the workplace are not available, which is frequently the case. The detection of an abnormally high concentration of mineral particles compared to control subjects with no particular exposure allow to confirm past exposure to one or more mineral particles and help guiding the diagnosis in the case of complex pathologies (in particular interstitial lung diseases or bronchopulmonary cancer) [3,21,22]. The pathologies induced by mineral particles are mainly due to particles retained in the alveolar compartment, and not to particles that benefit from muco-ciliary



1 clearance in the weeks following exposure. Asbestos or silica, as well as many metals, are bio-  
2 persistent particles that can be identified in excess in biological samples when compared to reference  
3 levels established in control subjects, even more than 10 years after the end of the exposure [3,23].  
4 Thus, mineralogical analysis of biological samples, in particular of BAL, is useful during the  
5 exploration of pathologies potentially linked to these particles, on the condition that the samples are of  
6 sufficient quality to have a reliable result.

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8 Interpretating results from a mineralogical analysis is complex, especially because of possible false  
9 negatives which may be caused by a heterogeneous retention of mineral particles in the lung [24].  
10 Occupational exposures to mineral particles are generally lower than in previous decades, and therefore  
11 results showing moderate load of mineral particles are more and more frequent. Thus, it is required to  
12 be sure of the alveolar representativeness of the BAL to be able to conclude adequately. A  
13 mineralogical analysis is considered well conducted if the result can be interpreted correctly. Another  
14 frequent cause of false negative is an inadequate performance of BAL which prevent having reliable  
15 mineralogical analysis results. The volume injected in the lung and the BAL's yield are factors  
16 associated with samples of good cytological quality. However, in this study, almost 19% of the samples  
17 analyzed did not have this information which makes their interpretation difficult when the AM count is  
18 borderline (between 40 000-60 000 for non-smokers/ex-smokers and 90 000-180 000 for smokers).

19 This also points out the importance of knowing the patient's smoking status.  
20 Under 100mL of injected volume, nearly half of the samples had a NR or UR cytological qualification,  
21 even when they had good yield ( $\geq 30\%$ ). A possible explanation is the higher proportion of BAL with  
22 bronchial contamination which represents almost 23% of samples in the <100mL strata versus 14% and  
23 9% respectively in the 100-150mL and  $\geq 150$ mL strata. We hypothesized that the low quantity of the  
24 collected liquid had led to pool the two fractions, bronchial and alveolar, to ensure the minimal volume

1 requested for mineralogical analysis (at least 20ml) in addition to other usual analyses (microbiological  
2 examination and cytological formula).

3 BAL sample with more than 200mL of injected volume had worse yield which may explain the  
4 proportion of sample of lesser quality in this subgroup (proportion of yield <30% of 37% versus 20%  
5 and 21% respectively in the 100-150mL and  $\geq$ 150mL strata).

6 The main limitation of this study was that we did not have information on the potential difficulties that  
7 might have been encountered during the BAL procedure. However, the large number of BAL samples  
8 included provided good confidence in the results. Likewise, even though there was only one cytologist  
9 reading the samples, the systematic evaluation of the samples by the same cytologist decreased the risk  
10 of differential bias for the qualification of the samples. Moreover, as stated in the title, this study is  
11 exclusively addressed to an adult population.

12

13 In conclusion, to obtain a bronchoalveolar lavage of sufficient quality to be representative of the  
14 alveolar area for mineralogical analyses, it is recommended to inject at least 100mL of saline solution  
15 and have a yield  $\geq$ 60%. It is acceptable to inject at least 150mL and have a yield  $\geq$ 30%. Injected  
16 volume, yield, and smoking status should be reported in all mineralogical analysis requests.

17

18 **Ethical approval and consent to participate:** This study obtained approval from the appropriate  
19 ethical committee (Local ethical committee of the Intercommunal Hospital of Creteil, approval n°  
20 2021-10-05).

21

22 **Availability of data and materials:** The datasets analyzed during the current study are available from  
23 the corresponding author on reasonable request.

24

1 **Declarations of interest:** None.

2

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5

6 **Authors' contributions:**

7 M.F, J.TVN, L.M, J.C.P. conceived the study, and were involved in the study design.

8 M.F. performed data analysis and drafted the manuscript.

9 J.TVN, P.G, K.B, P.B. participated in data collection.

10 M.F, J.TVN, P.G, K.B, P.B, F.S, G.M, B.M, J.B, L.M, J.C.P. analysed results.

11 M.F, J.TVN, F.S, G.M, B.M, J.B, L.M, J.C.P. critically reviewed the manuscript.

12 All authors read and approved the final manuscript.

13

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Table 1: Cytological qualification of BAL for mineralogical analyses

| Number of alveolar macrophages by mL                       | Non-smoker or Ex-smoker | < 25 000  | ≥ 25 000 - < 40 000 |           | ≥ 40 000 - < 60 000  |           | ≥ 60 000  |           |
|------------------------------------------------------------|-------------------------|-----------|---------------------|-----------|----------------------|-----------|-----------|-----------|
|                                                            | Smoker                  | < 60 000  | ≥ 60 000 - < 90 000 |           | ≥ 90 000 - < 180 000 |           | ≥ 180 000 |           |
| <b>Score</b>                                               |                         | 0         | 4                   |           | 5                    |           | 6         |           |
| <b>Bronchial contamination</b><br>≥ 30 % = -3 ; < 30 % = 0 |                         | -         | -3                  | 0         | -3                   | 0         | -3        | 0         |
| <b>Total Score</b>                                         |                         | 0         | 1                   | 4         | 2                    | 5         | 3         | 6         |
| <b>Conclusion*</b><br>NR = 0-1; UR = 2-3; RS = 4-6         |                         | <b>NR</b> | <b>NR</b>           | <b>RS</b> | <b>UR</b>            | <b>RS</b> | <b>UR</b> | <b>RS</b> |

\* Non-representative sample (NR), uncertain representativeness (UR) or representative sample (RS)

Table 2: Descriptive table and univariate analyses by BAL qualification

|                                              | Total*      | NR**        | UR**        | RS**        | P-value |
|----------------------------------------------|-------------|-------------|-------------|-------------|---------|
|                                              | N = 780     | N = 140     | N = 138     | N = 502     |         |
| Sex                                          |             |             |             |             | 0.690   |
| Female                                       | 73 (9.36%)  | 11 (15.1%)  | 15 (20.5%)  | 47 (64.4%)  |         |
| Male                                         | 707 (90.6%) | 129 (18.2%) | 123 (17.4%) | 455 (64.4%) |         |
| Age (in years)                               | 67.3 (12.3) | 68.4 (11.6) | 68.3 (11.7) | 66.8 (12.5) | 0.239   |
| Smoking status                               |             |             |             |             | /       |
| Non-smoker or Ex-smoker                      | 602 (77.2%) | 103 (17.1%) | 119 (19.8%) | 380 (63.1%) |         |
| Smoker                                       | 149 (19.8%) | 36 (24.2%)  | 13 (8.72%)  | 100 (67.1%) |         |
| Pack-years                                   | 29.0 (6.20) | 26.7 (6.13) | 28.6 (5.90) | 29.7 (6.14) | <0.001  |
| Disease reported                             |             |             |             |             | .       |
| Interstitial pneumonia                       | 398 (56.0%) | 65 (16.3%)  | 66 (16.6%)  | 267 (67.1%) |         |
| Nodules or micronodules                      | 100 (14.1%) | 17 (17.0%)  | 21 (21.0%)  | 62 (62.0%)  |         |
| Pleural plaques                              | 58 (8.16%)  | 11 (19.0%)  | 10 (17.1%)  | 37 (63.8%)  |         |
| Silicosis                                    | 26 (3.66%)  | 7 (26.9%)   | 1 (3.85%)   | 18 (69.2%)  |         |
| Lung cancer                                  | 25 (3.52%)  | 5 (20.0%)   | 5 (20.0%)   | 15 (60.0%)  |         |
| Adenopathies                                 | 21 (2.95%)  | 7 (33.3%)   | 7 (33.3%)   | 7 (33.3%)   |         |
| Asbestosis                                   | 20 (2.81%)  | 5 (25.0%)   | 5 (25.0%)   | 10 (50.0%)  |         |
| Pleural thickening                           | 15 (2.11%)  | 3 (20.0%)   | 2 (13.3%)   | 10 (66.7%)  |         |
| Pleural effusion                             | 15 (2.11%)  | 2 (13.3%)   | 5 (33.3%)   | 8 (53.3%)   |         |
| Mesothelioma                                 | 5 (0.70%)   | 1 (20.0%)   | 0 (0.00%)   | 4 (80.0%)   |         |
| Chronic obstructive pulmonary disease        | 5 (0.70%)   | 2 (40.0%)   | 0 (0.00%)   | 3 (60.0%)   |         |
| Sclerodermia                                 | 4 (0.56%)   | 0 (0.00%)   | 0 (0.00%)   | 4 (100%)    |         |
| Other                                        | 19 (2.67%)  | 4 (21.1%)   | 4 (21.1%)   | 11 (57.9%)  |         |
| Injected volume (mL)                         | 137 (42.2)  | 124 (47.0)  | 134 (42.7)  | 142 (39.8)  | <0.001  |
| Recovered volume (mL)                        | 58.8 (26.7) | 41.6 (24.5) | 52.6 (23.2) | 65.2 (25.6) | <0.001  |
| Yield                                        | 0.44 (0.16) | 0.36 (0.18) | 0.40 (0.13) | 0.47 (0.15) | <0.001  |
| Number of macrophages (x10 <sup>3</sup> /mL) | 272 (437)   | 28.1 (42.3) | 84.6 (64.3) | 388 (503)   | /       |
| Bronchial contamination                      |             |             |             |             | /       |
| No                                           | 683 (87.6%) | 87 (12.7%)  | 95 (13.9%)  | 501 (73.4%) |         |
| Yes                                          | 97 (12.4%)  | 53 (54.6%)  | 43 (44.3%)  | 1 (1.03%)   |         |
| Injected volume (categorised)                |             |             |             |             | <0.001  |
| < 100mL                                      | 71 (11.0%)  | 27 (38.0%)  | 12 (16.9%)  | 32 (45.1%)  |         |
| 100-150mL                                    | 181 (28.1%) | 40 (22.1%)  | 33 (18.2%)  | 108 (59.7%) |         |
| ≥ 150mL                                      | 391 (60.8%) | 53 (13.6%)  | 58 (14.8%)  | 280 (71.6%) |         |
| Yield (categorised)                          |             |             |             |             | <0.001  |
| < 30%                                        | 122 (19.2%) | 44 (36.1%)  | 22 (18.0%)  | 56 (45.1%)  |         |
| 30-60%                                       | 395 (62.2%) | 58 (14.7%)  | 75 (19.0%)  | 262 (66.3%) |         |
| ≥ 60%                                        | 118 (18.6%) | 15 (12.7%)  | 5 (4.24%)   | 98 (83.1%)  |         |

\* Qualitative variables are presented in number of subjects (%) and quantitative variables are presented in mean (standard deviation).

\*\* Non-representative sample (NR), uncertain representativeness (UR) or representative sample (RS)



Table 3: Yield and qualification of BAL stratified on injected volume

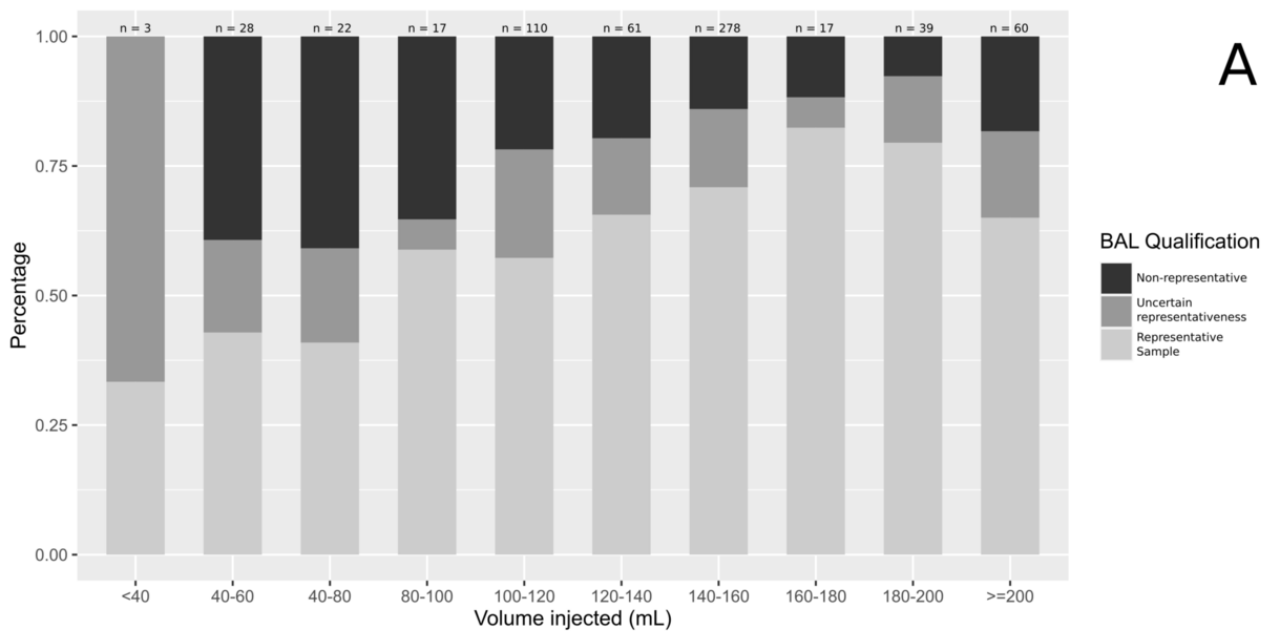
| <i>Injected volume &lt; 100mL</i> |            |             |            |         |
|-----------------------------------|------------|-------------|------------|---------|
|                                   | Yield      |             |            | P-value |
| <i>BAL qualification*</i>         | < 30%      | 30-60%      | ≥ 60%      | 0.676   |
| <i>NR</i>                         | 4 (57.1%)  | 14 (31.8%)  | 8 (42.1%)  |         |
| <i>UR</i>                         | 1 (14.3%)  | 9 (20.5%)   | 2 (10.5%)  |         |
| <i>RS</i>                         | 2 (28.6%)  | 21 (47.7%)  | 9 (47.4%)  |         |
| <i>Injected volume 100-150mL</i>  |            |             |            |         |
|                                   | Yield      |             |            |         |
| <i>BAL qualification*</i>         | < 30%      | 30-60%      | ≥ 60%      | <0.001  |
| <i>NR</i>                         | 15 (39.5%) | 22 (20.6%)  | 3 (8.82%)  |         |
| <i>UR</i>                         | 9 (23.7%)  | 23 (21.5%)  | 1 (2.94%)  |         |
| <i>RS</i>                         | 14 (36.8%) | 62 (57.9%)  | 30 (88.2%) |         |
| <i>Injected volume ≥ 150mL</i>    |            |             |            |         |
|                                   | Yield      |             |            |         |
| <i>BAL qualification*</i>         | < 30%      | 30-60%      | ≥ 60%      | <0.001  |
| <i>NR</i>                         | 25 (32.5%) | 22 (9.02%)  | 4 (6.15%)  |         |
| <i>UR</i>                         | 12 (15.6%) | 43 (17.6%)  | 2 (3.08%)  |         |
| <i>RS</i>                         | 40 (51.9%) | 179 (73.4%) | 59 (90.8%) |         |

\* Non-representative sample (NR), uncertain representativeness (UR) or representative sample (RS)

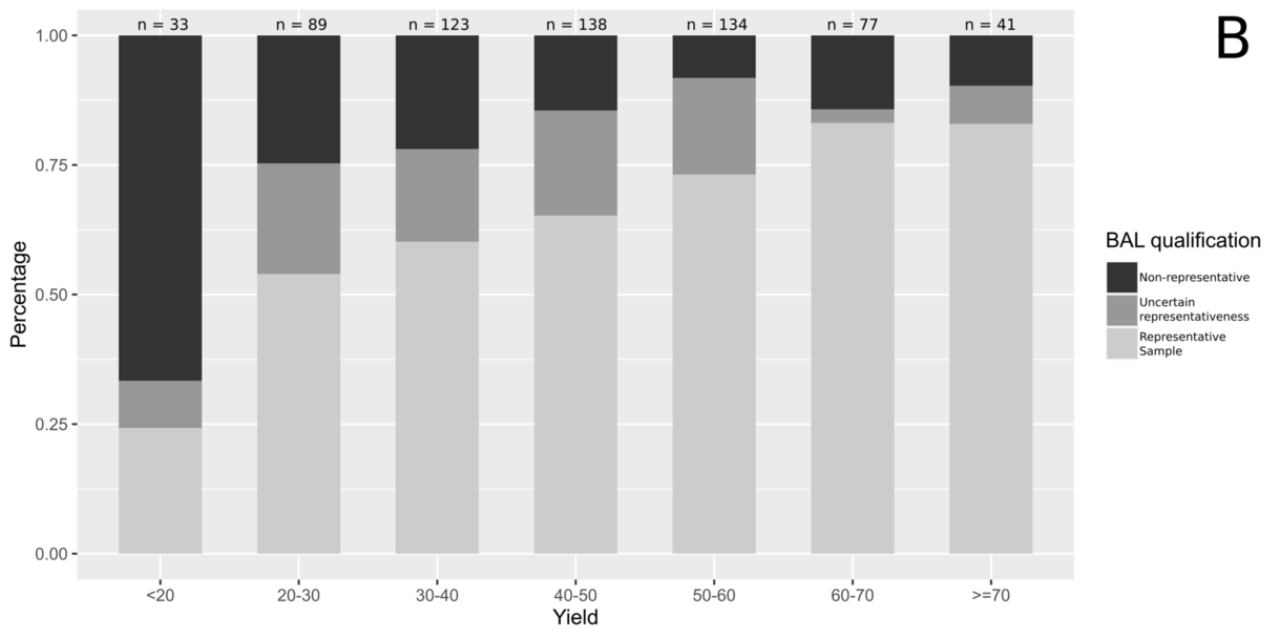
Figure 1: Distribution of the cytological qualification of BAL\* by (A) injected volume and (B) yield

Figure 2: Distribution of the cytological qualification of BAL\* by yield categories stratifies on volume injected

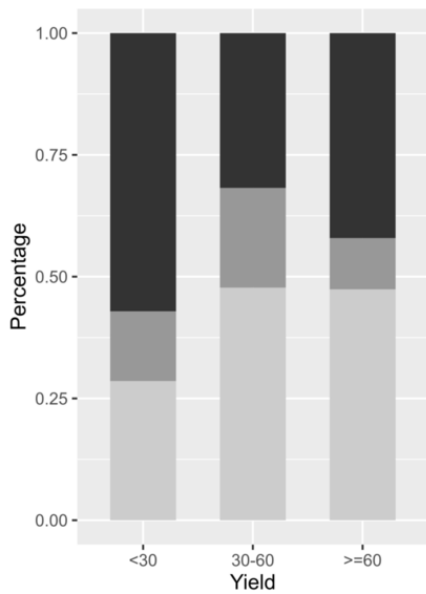
A



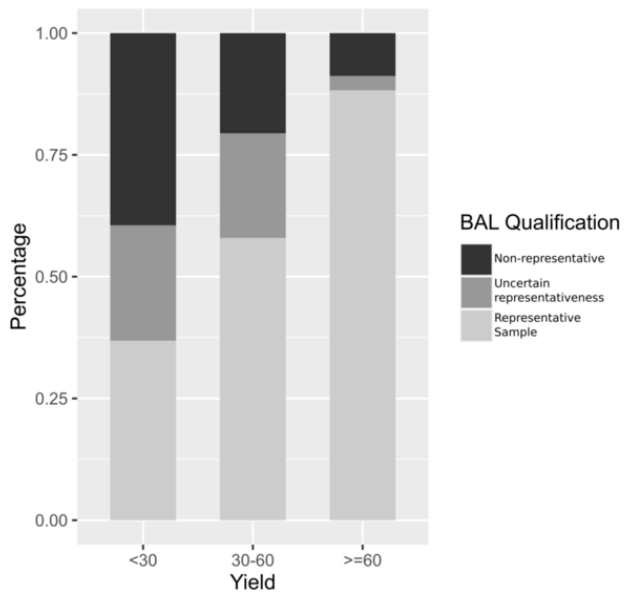
B



Volume injected <100mL



Volume injected 100-150mL



Volume injected >=150mL

